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(54) Title: CHEMICALLY-MODIFIED MYELOPOIETIN CONJUGATES

(57) Abstract: The present invention provides a chemically modified Myelopoietin (MPO) prepared by binding a water soluble polymer to the protein. The chemically-modified protein according to the present invention may have a much longer lasting neutrophil-increasing activity than that of the un-modified MPO, enabling reduced dose and scheduling opportunities.

CHEMICALLY-MODIFIED MYELOPOIETIN CONJUGATES

The present application claims priority under Title 35, United States Code, §119 of United States Provisional application Serial No. 60/195,496 filed April 06, 2000.

FIELD OF THE INVENTION

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The present invention relates to a chemical modification of myelopoietins (MPOs), a family of recombinant proteins, which are multifunctional agonists of human interleukin-3 (IL-3) and another hematopoietic growth factor receptor, including but not limited to G-CSF, by which the chemical and/or physiological properties of MPO can be changed. The PEGylated MPOs may have a decreased clearance rate, improved stability, decreased antigenicity, or a combination thereof. The family of MPO proteins is defined as the multifunctional agonists described in US 5,738,849, US 5,858,347, US 6,057,133, US 6,132,991, US 6,022,535, US 6,030,812, WO 95/21197 and WO 95/21256, which are incorporated herein in their entirety. The present invention also relates to processes for the modification of MPO. In addition, the present invention relates to pharmaceutical compositions comprising the modified MPO. A further embodiment is the use of the modified MPO to treat hematopoietic disorders.

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BACKGROUND OF THE INVENTION

Myelopoietin may be useful in the treatment of general haematopoietic disorders, including those arising from chemotherapy or from radiation therapy

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(Mac Vittie, T. J.; et al., Exp. Hematol. (1999), 27(10), 1557-1568). MPO may also be useful in bone marrow transplantation, wound healing, burn treatment, and the treatment of parasite, bacterial or viral infection.

It is generally observed that physiologically active proteins administered into a body can show their pharmacological activity only for a short period due to their high clearance rate in the body. Furthermore, the relative hydrophobicity of these proteins may limit their stability.

For the purpose of decreasing the clearance rate, improving stability or abolishing antigenicity of therapeutic proteins, some methods have been proposed wherein the proteins are chemically modified with water-soluble polymers. Chemical modification of this type may block effectively a proteolytic enzyme from physical contact with the protein backbone itself, thus preventing degradation. Chemical attachment may effectively reduce renal clearance. Additional advantages include, under certain circumstances, increasing the stability and circulation time of the therapeutic protein, increasing solubility, and decreasing immunogenicity. A review article describing protein modification and fusion proteins is Francis, Focus on Growth Factors 3: 4-10 (May 1992) (published by Mediscript, Mountview Court, Friern Barnet Lane, London N20, OLD, UK).

Poly(alkylene oxide), notably poly(ethylene glycol) (PEG), is one such chemical moiety, which has been used in the preparation of therapeutic protein products (the verb "pegylate" meaning to attach at least one PEG molecule). The attachment of poly(ethylene glycol) has been shown to protect against

proteolysis, Sada, et al., J. Fermentation

Bioengineering 71: 137-139 (1991), and methods for
attachment of certain poly(ethylene glycol) moieties
are available. See U.S. Pat. No. 4,179,337, Davis et
al., "Non-Immunogenic Polypeptides," issued Dec. 18,
1979; and U.S. Pat. No. 4,002,531, Royer, "Modifying
enzymes with Polyethylene Glycol and Product Produced
Thereby," issued Jan. 11, 1977. For a review, see
Abuchowski et al., in Enzymes as Drugs. (J. S.

10 Holcerberg and J. Roberts, eds. pp. 367-383 (1981)).

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Other water-soluble polymers have been used, such as copolymers of ethylene glycol/propylene glycol, carboxymethylcellulose, dextran, poly(vinyl alcohol), poly(vinyl pyrrolidone), poly(-1,3-dioxolane), poly(-1,3,6-trioxane), ethylene/maleic anhydride copolymer, poly- amino acids (either homopolymers or random copolymers).

A number of examples of pegylated therapeutic proteins have been described. ADAGEN®, a pegylated 20 formulation of adenosine deaminase, is approved for treating severe combined immunodeficiency disease. ONCASPAR®, a pegylated L-asparaginase has been approved for treating hypersensitive ALL patients. Pegylated superoxide dismutase has been in clinical trials for 25 treating head injury. Pegylated α -interferon (U.S. 5,738,846, 5,382,657) has been tested in phase III clinical trials for treating hepatitis with PEG-Intron (pegitron alfa-2b) approved for the treatment of chronic hepatitis C while another molecule, PEGASYS™, still awaits regulatory approval; pegylated 30 glucocerebrosidase and pegylated hemoglobin are reported to have been in preclinical testing. Another example is pegylated IL-6, EF 0 442 724, entitled,

"Modified hTL-6," which discloses poly(ethylene glycol) molecules added to IL-6.

Another specific therapeutic protein, which has been chemically modified, is granulocyte colony stimulating factor, (G-CSF). G-CSF induces the rapid proliferation and release of neutrophilic granulocytes to the blood stream, and thereby provides therapeutic effect in fighting infection. European patent publication EP 0 401 384, published Dec. 12, 1990, 10 entitled, "Chemically Modified Granulocyte Colony Stimulating Factor, " describes materials and methods for preparing G-CSF to which poly(ethylene glycol) molecules are attached. Modified G-CSF and analogs thereof are also reported in EP 0 473 268, published Mar. 4, 1992, entitled "Continuous Release 15 Pharmaceutical Compositions Comprising a Polypeptide Covalently Conjugated To A Water Soluble Polymer," stating the use of various G-CSF and derivatives covalently conjugated to a water soluble particle polymer, such as poly(ethylene glycol). A modified 20 polypeptide having human granulocyte colony stimulating factor activity is reported in EP 0 335 423 published Oct. 4, 1989. Provided in U.S. 5,824,784 are methods for N-terminally modifying proteins, including N-25 terminally chemically modified G-CSF compositions. U.S. 5,824,778 discloses chemically modified G-CSF.

Japanese patent application Hei2 (1990)-30555 discloses chemically modified human IL-3 having decreased antigenicity.

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The family of MPO proteins is disclosed in US 5,738,849, US 5,858,347, US 6,057,133, US 6,132,991, US 6,022,535, US 6,030,812, WO 95/21197, and WO 95/21256.

For poly(ethylene glycol), a variety of means has been used to attach the poly(ethylene glycol) molecules

to the protein. Generally, poly(ethylene glycol) molecules are connected to the protein via a reactive group found on the protein.

Amino groups, such as those on lysine residues or at the N-terminus, are convenient for such attachment. For example, Royer (U.S. Pat. No. 4,002,531, above) states that reductive alkylation was used for attachment of poly(ethylene glycol) molecules to an enzyme. EP 0 539 167, published Apr. 28, 1993, Wright, 10 "Peg Imidates and Protein Derivatives Thereof" states that peptides and organic compounds with free amino group(s) are modified with an imidate derivative of PEG or related water-soluble organic polymers. Chamow et al., Bioconjugate Chem. 5: 133-140 (1994) report the modification of CD4 immunoadhesin with 15 monomethoxypoly(ethylene glycol)aldehyde via reductive alkylation. The authors report that 50% of the CD4-Ig was MePEG-modified under conditions allowing control over the extent of pegylation. Ibid. at page 137. The 20 authors also report that the in vitro binding capability of the modified CD4-Ig (to the protein gp 120) decreased at a rate correlated to the extent of MePEGylation Ibid. U.S. Pat. No. 4,904,584, Shaw, issued Feb. 27, 1990, relates to the modification of the number of lysine residues in proteins for the 25 attachment of poly(ethylene glycol) molecules via reactive amine groups.

Many methods of attaching a polymer to a protein involve using a moiety to act as a linking group.

30 However, such moieties may be antigenic. A tresyl chloride method involving no linking group is available, but this method may be difficult to use to produce therapeutic products as the use of tresyl chloride may produce toxic by-products. See Francis et

al., In: Stability of protein pharmaceuticals: in vivo pathways of degradation and strategies for protein stabilization (Eds. Ahern. T. and Manning, M. C.)

Plenum, New York, 1991) Also, Delgado et al., "Coupling of PEG to Protein By Activation With Tresyl Chloride, Applications In Immunoaffinity Cell Preparation", in Separations Using Aqueous Phase Systems, Applications In Cell Biology and Biotechnology, Fisher et al., eds. Plenum Press, New York, N.Y., 1989 pp. 211-213.

See also, Rose et al., Bioconjugate Chemistry 2: 154-159 (1991) which reports the selective attachment of the linker group carbohydrazide to the C-terminal carboxyl group of a protein substrate (insulin).

The present invention provides chemically modified MPO molecules having decreased clearance rate, increased stability, decreased antigenicity, or combinations thereof.

SUMMARY OF THE INVENTION

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The present invention relates to chemically modified MPOs, which have at least one improved chemical or physiological property selected from but not limited to decreased clearance rate, increased stability, and decreased antigenicity. Thus, as described below in more detail, the present invention has a number of aspects relating to chemically modifying MPOs as well as specific modifications using a variety of poly(ethylene glycol) moieties.

The present invention also relates to methods of producing the chemically modified MPOs.

The present invention also relates to compositions comprising the chemically modified MPOs.

The modified MPO of the present invention may be useful in the treatment of, but not limited to, neutropenia, thrombocytopenia, mobilization of hematopoietic progenitors and stem cells into peripheral blood, bone marrow suppression or hematopoietic deficiencies, and immunodeficiencies.

BRIEF DESCRIPTION OF THE DRAWINGS

- 10 FIG. 1 is a reproduction of the ion-exchange chromatography elution profile of a 30,000 MW PEG-ALD MPO reaction.
- FIG. 2 is an SDS-PAGE of 20,000 and 30000 MW PEG-ALD MPO. Lane 1. MW Protein standards; Lane 2. MPO (10ug); Lane 3. 20,000 MW PEG-ALD MPO (10ug); Lane 4. 30,000 MW PEG-ALD MPO (10ug).
- FIG. 3a is an SEC HPLC profile of recombinant MPO 30,000 NW PEG-ALD RX mix, ion exchange purified N-terminally mono-pegylated 30,000 MW PEG-ALD MPO, recombinant MPO 20,000 MW PEG-ALD RX mix, and ion exchange purified N-terminally mono-pegylated 20,000 MW PEG-ALD MPO.
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- FIG. 3b is an SEC HPLC profile of 10,000 MW branched PEG2-NHS MPO, 20,000 MW branched PEG2-NHS MPO, and 40,000 MW branched PEG2-NHS MPO.
- 30 FIG. 4 is reversed phase HPLC profile for 1. MPO; 2. N-terminally mono-PEGylated 20,000 MW PEG-ALD MPO; and 3. N-terminally mono-PEGylated 30,000 MW PEG-ALD MPO.

FIG. 5 shows a reversed phase HPLC tryptic maps for MPO, N-terminally mono-PEGylated 30,000 MW PEG-ALD MPO, and N-terminally mono-PEGylated 20,000 MW PEG-ALD MPO.

5 FIG. 6 illustrates a comparison of response curves for an IL3 receptor agonist, a G-CSF receptor agonist, coaddition of IL3 receptor agonist and a G-CSF receptor agonist, un-PEGylated MPO and mono-PEGylated PEG-ALD MPO in colony forming unit granulocyte/macrophage (CFU-GM) assay which measures expansion and differentiation of a human bone marrow-derived CD34+ cells.

FIG. 7 compares the *in vivo* bioactivity of un-PEGylated and N-terminally mono-PEGylated PEG-ALD MPO by

15 illustrating the absolute neutrophil counts (ANC) during a period of 240 hours after a single subcutaneous injection dose in normal rhesus monkeys.

DETAILED DESCRIPTION OF THE INVENTION

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Myelopoietin (MPO) proteins are members of a family of recombinant proteins, which are multifunctional agonists of human interleukin-3 (IL-3) and another hematopoietic growth factor. Their recombinant production and methods of use are detailed in US 5,738,849, US 5,858,347, US 6,057,133, US 6,132,991, US 6,022,535, US 6,030,812, WO 95/21197 and WO 95/21256.

Any purified and isolated MPO, which is produced by host cells such as *E. coli* and animal cells transformed or transfected by using recombinant genetic techniques, may be used in the present invention. Among them, MPO, which is produced by the transformed E. coli, is particularly preferable. Such MPO may be

obtained in large quantities with high purity and homogeneity. For example, the above MPO may be prepared according to a method disclosed in US 5,738,849, US 5,858,347, US 6,057,133, US 6,132,991, US 6,022,535, and US 6,030,812. The term "substantially has the following amino acid sequence" means that the above amino acid sequence may include one or more amino-acid changes (deletion, addition, insertion or replacement) as long as such changes will not cause any disadvantageous non-similarity in function to MPO. It is more preferable to use the MPO substantially having an amino acid sequence, in which at least one lysine, aspartic acid, glutamic acid, or unpaired cysteine

residue is included.

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According to the present invention, poly(ethylene glycol) is covalently bound through amino acid residues of MPO. The amino acid residue may be any reactive one(s) having, for example, free amino, carboxyl or sulfhydryl (thiol) groups, to which a terminal reactive group of an activated poly(ethylene glycol) may be bound. The amino acid residues having the free amino groups may include lysine residues and/or N-terminal amino acid residue, those having a free carboxyl group may include aspartic acid, glutamic acid and/or C-terminal amino acid residues, and having a sulfhydryl (thiol) such as cysteine.

In another embodiment, oxine chemistries (Lemieux & Bertozzi *Tib Tech* **16**:506-513, 1998) are used to target N-terminal serine residues.

The poly(ethylene glycol) used in the present invention is not restricted to any particular form or molecular weight range. Normally a molecular weight of 500-60,000 is used and preferably of from 1,000-40,000. The poly(ethylene glycol) can also be a branched PEG as

described in U.S. 5,932,462, U.S. 5,342,940, U.S. 5,643,575, U.S. 5,919,455, U.S. 6,113,906, and U.S. 5,183,660.

Poly(alkylene oxides), notably poly(ethylene glycol)s, are bound to MPO via a terminal reactive 5 group, which may or may not leave a linking moiety (spacer) between the PEG and the protein. In order to form the MPO conjugates of the present invention, polymers such as poly(alkylene oxide) are converted into activated forms, as such term is known to those of 10 ordinary skill in the art. The reactive group, for example, is a terminal reactive group, which mediates a bond between chemical moieties on the protein, such as amino, carboxyl or thiol groups, and poly(ethylene glycol). Typically, one or both of the terminal polymer 15 hydroxyl end-groups, (i.e. the alpha and omega terminal hydroxyl groups) are converted into reactive functional groups, which allows covalent conjugation. This process is frequently referred to as "activation" and the poly(ethylene glycol) product having the reactive group 20 is hereinafter referred to as "an activated poly(ethylene glycol)". Polymers containing both α and ω linking groups are referred to as "bis-activated poly(alkylene oxides)" and are referred to as "bifunctional". Polymers containing the same reactive 25 group on α and ω terminal hydroxyls are sometimes referred to as "homobifunctional" or "homobisactivated". Polymers containing different reactive groups on α and ω terminal hydroxyls are sometimes 30 referred to as "heterobifunctional" or "heterobisactivated". Polymers containing a single reactive group are referred to as "mono-activated" polyalkylene oxides or "mono-functional". Other substantially non-

antigenic polymers are similarly "activated" or "functionalized".

The activated polymers are thus suitable for mediating a bond between chemical moieties on the protein, such as α -amino, carboxyl or thiol groups, and poly(ethylene glycol). Bis-activated polymers can react in this manner with two protein molecules or one protein molecule and a reactive small molecule in another embodiment to effectively form protein polymers or protein-small molecule conjugates through cross 10 linkages. Functional groups capable of reacting with either the amino terminal α -amino group or ϵ -amino groups of lysines found on the MPO include: carbonates such as the p-nitrophenyl, or succinimidyl; carbonyl imidazole; azlactones; cyclic imide thiones; 15 isocyanates or isothiocyanates and aldehydes. Functional groups capable of reacting with carboxylic acid groups, reactive carbonyl groups and oxidized carbohydrate moieties on MPO include; primary amines; and hydrazine and hydrazide functional groups such as 20 the acyl hydrazides, carbazates, semicarbamates, thiocarbazates, etc. Mercapto groups, if available on the MPO, can also be used as attachment sites for suitably activated polymers with reactive groups such as thiols; maleimides, sulfones, and phenyl glyoxals; 25 see, for example, U.S. Pat. No. 5,093,531, the disclosure of which is hereby incorporated by reference. Other nucleophiles capable of reacting with an electrophilic center include, but are not limited to, for example, hydroxyl, amino, carboxyl, thiol, 30 active methylene and the like.

In one preferred embodiment of the invention secondary amine or amide linkages are formed using the MPO N-terminal amino groups or \(\epsilon\)-amino groups of lysine

and the activated PEG. In another preferred aspect of the invention, a secondary amine linkage is formed between the N-terminal primary amino group of MPO and single or branched chain PEG aldehyde by reduction with a suitable reducing agent such as NaCNBH3, NaBH3, Pyridine Borane etc. as described in Chamow et al., Bioconjugate Chem. 5: 133-140 (1994) and US Pat. No 5,824,784.

In another preferred embodiment of the invention, polymers activated with amide-forming linkers such as 10 succinimidyl esters, cyclic imide thiones, or the like are used to effect the linkage between the MPO and polymer, see for example, U.S. Pat. No. 5,349,001; U.S. Pat. No. 5,405,877; and Greenwald, et al., Crit. Rev. 15 Ther. Drug Carrier Syst. 17:101-161, 2000, which are incorporated herein by reference. One preferred activated poly(ethylene glycol), which may be bound to the free amino groups of MPO includes single or branched chain N-hydroxysuccinylimide poly(ethylene glycol) may be prepared by activating succinic acid 20 esters of poly(ethylene glycol) with Nhydroxysuccinylimide.

Other preferred embodiments of the invention include using other activated polymers to form covalent linkages of the polymer with the MPO via \(\epsilon\)-amino or other groups. For example, isocyanate or isothiocyanate forms of terminally activated polymers can be used to form urea or thiourea-based linkages with the lysine amino groups.

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In another preferred aspect of the invention, carbamate (urethane) linkages are formed with protein amino groups as described in U.S. Pat. Nos. 5,122,614, 5,324,844, and 5,612,640, which are hereby incorporated by reference. Examples include N-succinimidyl

carbonate, para-nitrophenyl carbonate, and carbonyl imidazole activated polymers. In another preferred embodiment of this invention, a benzotriazole carbonate derivative of PEG is linked to amino groups on MPO.

5 Another aspect of the invention represents a prodrug or sustained release form of MPO, comprised of a water soluble polymer, such as poly(ethylene glycol), attached to an MPO molecule by a functional linker that can predictably break down by enzymatic or pH directed hydrolysis to release free MPO or other MPO derivative. 10 The prodrug can also be a "double prodrug" (Bundgaard in Advanced Drug Delivery Reviews 3:39-65, 1989) involving the use of a cascade latentiation. In such systems, the hydrolytic reaction involves an initial 15 rate-limiting (slow) enzymatic or pH directed step and a second step involving a rapid non-enzymatic hydrolysis that occurs only after the first has taken place. Such a releasable polymer provides protein conjugates, which are impermanent and could act as a 20 reservoir, that continually discharge MPO. Such functional linkers are described in US 5,614,549; US 5,840,900; US 5,880,131; US 5,965,119; US 6,011,042; US 6,180,095 B1; Greenwald R.B. et al., J. Med. Chem. 42;3657-3667, 1999; Lee, S. et al., Bioconjugate Chem 12:163-169, 2001; Garman A.J. et al., FEBS Lett. 25 223:361-365, 1987; Woghiren C. et al., Bioconjucate Chem. 4:314-318, 1993; Roberts M.J. et al., J. Pharm. Sci. 87;1440-1445, 1998; Zhao X., in Ninth Int. Symp. Recent Adv. Drug Delivery Syst. 199; Greenwald R.B. et 30 al., J. Med. Chem. 43:475-487, 2000; and Greenwald R.B. Crit. Rev. Ther. Drug Carrier Syst. 17:101-161, 2000.

Conjugation reactions, referred to as pegylation reactions, were historically carried out in solution

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with molar excess of polymer and without regard to where the polymer will attach to the protein. Such general techniques, however, have typically been proven inadequate for conjugating bioactive proteins to non-antigenic polymers while retaining sufficient bioactivity. One way to maintain the MPO bioactivity is to substantially avoid the conjugation of those MPO reactive groups associated with the receptor binding site(s) in the polymer coupling process. Another aspect of the present invention is to provide a process of conjugating poly(ethylene glycol) to MPO maintaining high levels of retained activity.

The chemical modification through a covalent bond may be performed under any suitable condition generally 15 adopted in a reaction of a biologically active substance with the activated poly(ethylene glycol). The conjugation reaction is carried out under relatively mild conditions to avoid inactivating the MPO. Mild conditions include maintaining the pH of the reaction 20 solution in the range of 3 to 10 and the reaction temperatures within the range of from about 0°-37°C. In the cases where the reactive amino acid residues in MPO have free amino groups, the above modification is preferably carried out in a non-limiting list of suitable buffers (pH 3 to 10), including phosphate, 25 citrate, acetate, succinate or HEPES, for 1-48 hrs at 4° -37°C. In targeting N-terminal amino groups with reagents such as PEG aldehydes pH 4-7 is preferably maintained. The activated poly(ethylene glycol) may be used in 0.05-100 times, preferably 0.05-0.5 times, the 30 molar amount of the number of free amino groups of MPO. On the other hand, where reactive amino acid residues in MPO have the free carboxyl groups, the above modification is preferably carried out in pH from about

3.5 to about 5.5, for example, the modification with poly(oxyethylenediamine) is carried out in the presence of carbodiimide (pH 4-5) for 1-24 hrs at 4°-37°C. The activated poly(ethylene glycol) may be used in 0.05-300 times the molar amount of the number of free carboxyl groups of MPO.

In separate embodiments, the upper limit for the amount of polymer included in the conjugation reactions exceeds about 1:1 to the extent that it is possible to react the activated polymer and MPO without forming a substantial amount of high molecular weight species, i.e. more than about 20% of the conjugates containing more than about one strand of polymer per molecule of MPO. For example, it is contemplated in this aspect of the invention that ratios of up to about 6:1 can be employed to form significant amounts of the desired conjugates which can thereafter be isolated from any high molecular weight species.

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In another aspect of this invention, bifunctionally activated PEG derivatives may be used to 20 generate polymeric MPO-PEG molecules in which multiple MPO molecules are crosslinked via PEG. Although the reaction conditions described herein can result in significant amounts of unmodified MPO, the unmodified MPO can be readily recycled into future batches for 25 additional conjugation reactions. The processes of the present invention generate surprisingly very little, i.e. less than about 30% and more preferably, less than about 10%, of high molecular weight species and species 30 containing more than one polymer strand per MPO. These reaction conditions are to be contrasted with those typically used for polymeric conjugation reactions wherein the activated polymer is present in severalfold molar excesses with respect to the target. In

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other aspects of the invention, the polymer is present in amounts of from about 0.1 to about 50 equivalents per equivalent of MPO. In other aspects of the invention, the polymer is present in amounts of from about 1 to about 10 equivalents per equivalent of MPO.

The conjugation reactions of the present invention initially provide a reaction mixture or pool containing mono- and di-PEG-MPO conjugates, unreacted MPO, unreacted polymer and usually less than about 20% high 10 molecular weight species. The high molecular weight species include conjugates containing more than one polymer strand and/or polymerized PEG-MPO species. After the unreacted species and high molecular weight species have been removed, compositions containing primarily mono- and di-polymer-MPO conjugates are 15 recovered. Given the fact that the conjugates for the most part include a single polymer strand, the conjugates are substantially homogeneous. These modified MPOs have at least about 5% of the in vitro biological activity associated with the native or 20 unmodified MPO as measured using standard cell proliferation assays, such as AML, TF1 and colony forming unit assays (U.S. Patent 6,030,812 which is incorporated by reference herein). In preferred aspects of the invention, however, the modified MPOs have about 25 25% of the in vitro biological activity, more preferably, the modified MPOs have about 50% of the in vitro biological activity, more preferably, the modified MPOs have about 75% of the in vitro biological activity, and most preferably the modified MPOs have 30 equivalent or improved in vitro biological activity.

The processes of the present invention preferably include rather limited ratios of polymer to MPO. Thus, the MPO conjugates have been found to be predominantly

limited to species containing only one strand of polymer. Furthermore, the attachment of the polymer to the MPO reactive groups is substantially less random than when higher molar excesses of polymer linker are used. The unmodified MPO present in the reaction pool, after the conjugation reaction has been quenched, can be recycled into future reactions using ion exchange or size exclusion chromatography or similar separation techniques.

A poly(ethylene glycol)-modified MPO, namely chemically modified protein according to the present invention, may be purified from a reaction mixture by conventional methods which are used for purification of proteins, such as dialysis, salting-out,

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ultrafiltration, ion-exchange chromatography, gel chromatography and electrophoresis. Ion-exchange chromatography is particularly effective in removing unreacted poly(ethylene glycol) and MPO. In a further embodiment of the invention, the mono- and di-polymer-MPO species are isolated from the reaction mixture to remove high molecular weight species, and unmodified MPO. Separation is effected by placing the mixed species in a buffer solution containing from about 0.5-10 mg/mL of the MPO-polymer conjugates. Suitable solutions have a pH from about 4 to about 10. The solutions preferably contain one or more buffer salts selected from KCl, NaCl, K2HPO4, KH2PO4, Na2HPO4, NaH2PO4, NaHCO3, NaBO4, CH3CO2H, and NaOH.

Depending upon the reaction buffer, the MPO polymer conjugate solution may first have to undergo buffer exchange/ultrafiltration to remove any unreacted polymer. For example, the PEG-MPO conjugate solution can be ultrafiltered across a low molecular weight cutoff (10,000 to 30,000 Dalton) membrane to remove most

unwanted materials such as unreacted polymer, surfactants, if present, or the like.

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The fractionation of the conjugates into a pool containing the desired species is preferably carried out using an ion exchange chromatography medium. Such media are capable of selectively binding PEG-MPO conjugates via differences in charge, which vary in a somewhat predictable fashion. For example, the surface charge of MPO is determined by the number of available charged groups on the surface of the protein. These charged groups typically serve as the point of potential attachment of poly(alkylene oxide) conjugates. Therefore, MPO conjugates will have a different charge from the other species to allow selective isolation.

Strongly polar anion or cation exchange resins such as quaternary amine or sulfopropyl resins, respectively, are used for the method of the present invention. Cation exchange resins are especially preferred. A non-limiting list of included commercially 20 available cation exchange resins suitable for use with the present invention are SP-hitrap®, SP Sepharose HP® and SP Sepharose® fast flow. Other suitable cation exchange resins e.g. S and CM resins can also be used. A non-limiting list of anion exchange resins, including 25 commercially available anion exchange resins, suitable for use with the present invention are Q-hitrap®, Q Sepharose HP®, and Q sepharose® fast flow. Other suitable anion exchange resins, e.g. DEAE resins, can 30 also be used.

For example, the cation exchange resin is preferably packed in a column and equilibrated by conventional means. A buffer having the same pH and osmolality as the polymer conjugated MPO solution is

used. The elution buffer preferably contains one or more salts selected from KCl, NaCl, K2HPO4, KH2PO4, Na_2HPO_4 , NaH_2PO_4 , $NaHCO_3$, $NaBO_4$ and $(NH_4)_2CO_3$. The conjugate-containing solution is then adsorbed onto the column with unreacted polymer and some high molecular 5 weight species not being retained. At the completion of the loading, a gradient flow of an elution buffer with increasing salt concentrations is applied to the column to elute the desired fraction of polyalkylene oxide-10 conjugated MPO. The eluted pooled fractions are preferably limited to uniform polymer conjugates after the cation exchange separation step. Any unconjugated MPO species can then be back washed from the column by conventional techniques. If desired, mono and multiply pegylated MPO species can be further separated from 15 each other via additional ion exchange chromatography or size exclusion chromatography. Techniques utilizing multiple isocratic steps of increasing concentration can also be used. Multiple 20 isocratic elution steps of increasing concentration will result in the sequential elution of di- and then mono-MPO-polymer conjugates.

The temperature range for elution is between about 4°C and about 25°C. Preferably, elution is carried out at a temperature of from about 6°C to about 22°C. For example, the elution of the PEG-MPO fraction is detected by UV absorbance at 280 nm. Fraction collection may be achieved through simple time elution profiles.

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A surfactant can be used in the processes of conjugating the poly(ethylene glycol) polymer with the MPO moiety. Suitable surfactants include ionic-type agents such as sodium dodecyl sulfate (SDS). Other ionic surfactants such as lithium dodecyl sulfate,

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quaternary ammonium compounds, taurocholic acid, caprylic acid, decane sulfonic acid, etc. can also be used. Non-ionic surfactants can also be used. For example, materials such as poly(oxyethylene) sorbitans (Tweens), poly(oxyethylene) ethers (Tritons) can be used. See also Neugebauer, A Guide to the Properties and Uses of Detergents in Biology and Biochemistry (1992) Calbiochem Corp. The only limitations on the surfactants used in the processes of the invention are that they are used under conditions and at concentrations that do not cause substantial irreversible denaturation of the MPO and do not completely inhibit polymer conjugation. The surfactants are present in the reaction mixtures in amounts from about 0.01-0.5%; preferably from 0.05-0.5%; and most preferably from about 0.075-0.25%. Mixtures of the surfactants are also contemplated.

It is thought that the surfactants provide a temporary, reversible protecting system during the polymer conjugation process. Surfactants have been shown to be effective in selectively discouraging polymer conjugation while allowing lysine-based or amino terminal-based conjugation to proceed.

The present poly(ethylene glycol)-modified MPO has a more enduring pharmacological effect, which may be possibly attributed to its prolonged half-life in vivo. Furthermore, it is observed that the present poly(ethylene glycol)-modified MPO may accelerate recovery from neutropenia.

The present poly(ethylene glycol)-modified MPO may have essentially the same biological activity as an intact MPO and may accordingly be used in the same applications. The poly(ethylene glycol)-modified MPO has an activity for increasing the number of

neutrophils, and it is useful therefore in the treatment of general hematopoietic disorders including those arising from chemotherapy or from radiation therapy. It may be also useful in the treatment of infection and in bone marrow transplantation. The modified MPO of the present invention may be useful in the treatment of diseases characterized by decreased levels of either myeloid, erythroid, lymphoid, or megakaryocyte cells of the hematopoietic system or combinations thereof. In addition, they may be used to 10 activate mature myeloid and/or lymphoid cells. Among conditions susceptible to treatment with the polypeptides of the present invention is leukopenia, a reduction in the number of circulating leukocytes (white cells) in the peripheral blood. Leukopenia may 15 be induced by exposure to certain viruses or to radiation. It is often a side effect of various forms of cancer therapy, e.g., exposure to chemotherapeutic drugs, radiation and of infection or hemorrhage. Therapeutic treatment of leukopenia with these modified 20 MPO of the present invention may avoid undesirable side effects caused by treatment with presently available

The modified MPO of the present invention may be
useful in the treatment or prevention of neutropenia
and, for example, in the treatment of such conditions
as aplastic anemia, cyclic neutropenia, idiopathic
neutropenia, Chediak-Higashi syndrome, systemic lupus
erythematosus (SLE), leukemia, myelodysplastic syndrome
and myelofibrosis.

drugs.

The modified MPO of the present invention may be useful in the treatment or prevention of thrombocytopenia. Currently the only therapies for thrombocytopenia are platelet transfusions, which are

costly and carry the significant risks of infection (HIV, HBV) and alloimmunization, and IL-11 (Neumega™), which is approved for certain thrombocytopenia. The modified MPO may alleviate or diminish the need for platelet transfusions. Severe thrombocytopenia may result from genetic defects such as Fanconi's Anemia, Wiscott-Aldrich, or May-Hegglin syndromes. Acquired thrombocytopenia may result from auto- or alloantibodies as in Immune Thrombocytopenia Purpura, Systemic Lupus Erythematosis, hemolytic anemia, or 10 fetal maternal incompatibility. In addition, splenomegaly, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, infection, or prosthetic heart valves may result in thrombocytopenia. Severe thrombocytopenia may also result from 15 chemotherapy and/or radiation therapy or cancer. Thrombocytopenia may also result from marrow invasion by carcinoma, lymphoma, leukemia, or fibrosis.

The modified MPO of the present invention may be useful in the mobilization of hematopoietic progenitors and stem cells into peripheral blood. Peripheral blood derived progenitors have been shown to be effective in reconstituting patients in the setting of autologous marrow transplantation. Hematopoietic growth factors including G-CSF and GM-CSF have been shown to enhance the number of circulating progenitors and stem cells in the peripheral blood. This has simplified the procedure for peripheral stem cell collection and dramatically decreased the cost of the procedure by decreasing the number of phereses required. The modified MPO may be useful in mobilization of stem cells and further enhance the efficacy of peripheral stem cell transplantation.

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Another projected clinical use of growth factors

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has been in the *in vitro* activation of hematopoietic progenitors and stem cells for gene therapy. In order to have the gene of interest incorporated into the genome of the hematopoietic progenitor or stem cell one needs to stimulate cell division and DNA replication. Hematopoietic stem cells cycle at a very low frequency, which means that growth factors may be useful to promote gene transduction and thereby enhance the clinical prospects for gene therapy.

Many drugs may cause bone marrow suppression or hematopoietic deficiencies. Examples of such drugs are AZT, DDI, alkylating agents and anti-metabolites used in chemotherapy, antibiotics such as chloramphenicol, penicillin, gancyclovir, daunomycin and sulfa drugs, phenothiazones, tranquilizers such as meprobamate, analgesics such as aminopyrine and dipyrone, anti-convulsants such as phenytoin or carbamazepine, antithyroids such as propylthiouracil and methimazole and diuretics. The modified MPO of the present invention may be useful in preventing or treating the bone marrow suppression or hematopoietic deficiencies, which often occur in patients treated with these drugs.

Hematopoietic deficiencies may also occur because of viral, microbial, or parasitic infections and as a result of treatment for renal disease or renal failure, e.g., dialysis. The modified MPO of the present invention may be useful in treating such hematopoietic deficiency.

The treatment of hematopoietic deficiency may include administration of a pharmaceutical composition containing the modified MPO to a patient. The modified MPO of the present invention may also be useful for the activation and amplification of hematopoietic precursor cells by treating these cells *in vitro* with the

modified MPO of the present invention prior to injecting the cells into a patient.

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Various immunodeficiencies e.g., in T and/or B lymphocytes, or immune disorders, e.g., rheumatoid arthritis, may also be beneficially affected by treatment with the modified MPO of the present Immunodeficiencies may be the result of invention. viral infections e.g. HTLV-I, HTLV-II, HTLV-III, severe exposure to radiation, cancer therapy or the result of other medical treatment. The modified MPO of the present invention may also be employed, alone or in combination with other hematopoietins, in the treatment of other blood cell deficiencies, including thrombocytopenia (platelet deficiency), or anemia. Other uses for these novel polypeptides are in the treatment of patients recovering from bone marrow transplants in vivo and ex vivo, and in the development of monoclonal and polyclonal antibodies generated by standard methods for diagnostic or therapeutic use.

20 The present poly(ethylene glycol)-modified MPO may be formulated into pharmaceuticals containing also a pharmaceutically acceptable diluent, an agent for preparing an isotonic solution, a pH-conditioner and the like in order to administer them into a patient.

25 The above pharmaceuticals may be administered subcutaneously, intramuscularly, intravenously, or orally, depending on a purpose of treatment. A dose may be also based on the kind and condition of the disorder of a patient to be treated, being normally between 0.1 mg and 50 mg by injection and between 0.1 mg and 5 g in an oral administration for an adult

The polymeric substances included are also preferably water-soluble at room temperature. A non-limiting list of such polymers include poly(alkylene

oxide) homopolymers such as poly(ethylene glycol) or poly(propylene glycols), poly(oxyethylenated polyols), copolymers thereof and block copolymers thereof, provided that the water solubility of the block copolymers is maintained.

As an alternative to PEG-based polymers, effectively non-antigenic materials such as dextran, poly(vinyl pyrrolidones), poly(acrylamides), poly(vinyl alcohols), carbohydrate-based polymers, and the like can be used. Indeed, the activation of α - and ω -10 terminal groups of these polymeric substances can be effected in fashions similar to that used to convert poly(alkylene oxides) and thus will be apparent to those of ordinary skill. Those of ordinary skill in the art will realize that the foregoing list is merely 15 illustrative and that all polymer materials having the qualities described herein are contemplated. For purposes of the present invention, "effectively nonantigenic" means all materials understood in the art as being nontoxic and not eliciting an appreciable 20 immunogenic response in mammals.

Definitions

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25 The following is a list of abbreviations and the corresponding meanings as used interchangeably herein:

g gram(s)

mg milligram(s)

ml or mL milliliter(s) .

30 RT room temperature

PEG poly (ethylene glycol)

The complete content of all publications, patents, and patent applications cited in this disclosure are

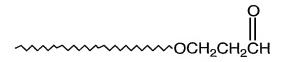
herein incorporated by reference as if each individual publication, patent, or patent application were specifically and individually indicated to be incorporated by reference.

Although the foregoing invention has been described in some detail by way of illustration and example for the purposes of clarity of understanding, it will be readily apparent to one skilled in the art in light of the teachings of this invention that changes and modifications can be made without departing from the spirit and scope of the present invention. The following examples are provided for exemplification purposes only and are not intended to limit the scope of the invention, which has been described in broad terms above.

In the following examples, the MPO polypeptide is that of residues 2-322 of SEQ ID NO:224. It is understood that other members of the MPO family of polypeptides could also be pegylated in a similar manner as exemplified in the subsequent examples.

EXAMPLE 1

Straight Chain 30,000 MW PEG-ALD MPO



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M-PEG-Aldehyde 5,000, 20,000 and 30,000 MW

This example demonstrates a method for generation of substantially homogeneous preparations of N-terminally monopegylated MPO by reductive alkylation. Methoxylinear PEG-propional dehyde reagent of approximately 30,000 MW (Shearwater Polymers Inc.) was selectively

coupled via reductive amination to the N-terminus of MPO by taking advantage of the difference in the relative pKa value of the primary amine at the Nterminus versus pKa values of primary amines at the &amino position of lysine residues. MPO protein dissolved at 4.5 mg/mL in 10-20 mM sodium acetate, pH 4.5, was reacted with Methoxy-PEGpropionaldehyde (M-PEG-ALD) by addition of solid M-PEG-ALD to yield a relative PEG: Myelopoietin molar ratio of 10 6.5:1. Reactions were catalyzed by addition of stock 1M NaCNBH₄ dissolved in H_2O to a final concentration of 20 mM. Reactions were carried out at 4°C for 18-96 hours. Reactions were stopped by lowering the pH to 4.0 with 0.1 N acetic acid or by adding a 5X molar excess 15 of Tris HCl.

EXAMPLE 2

Straight Chain 20,000 MW PEG-ALD MPO

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Methoxy-linear 20,000 MW PEG-propional dehyde reagent (Shearwater Polymers Inc.) was coupled to the N-terminus of MPO using the procedure described for Example 1.

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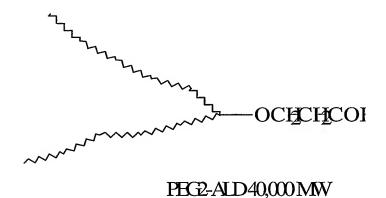
EXAMPLE 3

Straight chain 5,000 MW PEG-ALD MPO

30 Methoxy-linear 5,000 MW PEG-propional dehyde reagent (Fluka) was coupled to the N-terminus of MPO using the procedure described for Example 1.

EXAMPLE 4

Branched chain 40,000 MW PEG2-ALD MPO



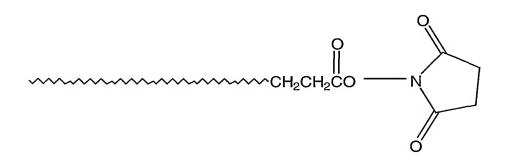
5

Methoxy-branched 40,000 MW PEG-propionaldehyde (PEG2-ALD) reagent (Shearwater Polymers Inc.) was coupled to the N-terminus of MPO using the procedure described for Example 1.

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EXAMPLE 5

Straight chain 20,000 MW PEG-SPA MPO



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PEG-SPA 5,000 and 20,000 MW

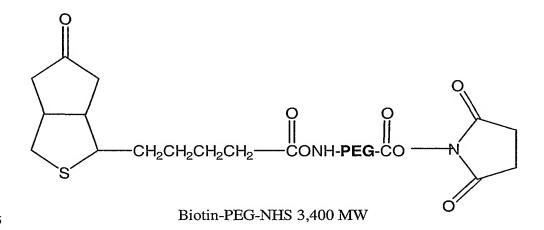
This example demonstrates a method for generation of substantially homogeneous preparations of monopegylated Myelopoietin (MPO) using N-hydroxysuccinimidyl (NHS) active esters. MPO protein stock solution dissolved at

4.5 mg/mL in 10-20 mM sodium acetate, pH 4.5 was titrated to pH 7.2 by addition of 0.25 M HEPES buffer. The solution was then reacted with Methoxy-PEG-succinimidyl propionate (SPA-PEG) by addition of solid SPA-PEG to yield a relative PEG:Myelopoietin molar ratio of 6.5:1. Reactions were carried out at 4°C for 1 hour. Reactions were stopped by lowering the pH to 4.0 with 0.1 N acetic acid or by adding a 5X molar excess of Tris HCl.

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EXAMPLE 6

Straight chain 3,400 MW Biotin-PEG-NHS MPO



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3,400 MW Biotin-PEG-CO₂-NHS reagent (Shearwater Polymers Inc.) was coupled to MPO using the procedure described for Example 5.

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EXAMPLE 7

Branched 10,000 MW PEG2-NHS MPO

PEG2-NHS 10,000, 20,000 and 40,000 MW

10,000 MW branched PEG2-NHS (Shearwater Polymers Inc.) was coupled to MPO using the procedure described for Example 5.

EXAMPLE 8

Branched 20,000 MW PEG2-NHS MPO

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20,000 MW branched PEG2-SPA (Shearwater Polymers Inc.) was coupled to MPO using the procedure described for Example 5.

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EXAMPLE 9

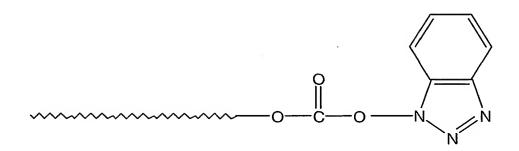
Branched 40,000 MW PEG2-NHS MPO

40,000 MW branched PEG2-NHS (Shearwater Polymers Inc.)
20 was coupled to MPO using the procedure described for Example 5.

EXAMPLE 10

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Straight chain 20,000 MW PEG-BTC MPO



PEG-BTC 20,000 NIV

20,000 MW PEG-BTC (Shearwater Polymers Inc.) was coupled to MPO using the procedure described for Example 4. This example demonstrates a method for generation of substantially homogeneous preparations of pegylated Myelopoietin (MPO) using benzotriazole carbonate derivatives of PEG.

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EXAMPLE 11

Straight chain 5,000 MW PEG-SS MPO

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PEG-SS 5,000 MW

5,000 MW succinimidyl succinate-PEG (PEG-SS) (Shearwater Polymers Inc.) was coupled to MPO using the procedure described for Example 5. This example demonstrates a method for generation of substantially homogeneous

preparations of monopegylated Myelopoietin (MPO) using a hydrolyzable linkage.

EXAMPLE 12

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Straight chain 20,000 MW PEG-HZ MPO

VVVVVVVVVOCH2CONHNH2

PEG-Hydrazide 20,000 MW

This example demonstrates a method for generation of substantially homogeneous preparations of pegylated Myelopoietin (MPO) using 20,000 MW methoxy-PEG-hydrazide, PEG-HZ (Shearwater Polymers Inc.). MPO protein stock solution dissolved at 4-8 mg/mL in 250 mM MES, pH 4 - 5. The solution was then reacted with PEG-HZ by addition of solid to yield a relative PEG:Myelopoietin molar ratio of 6.5 - 26:1 reactions were catalyzed with carbodiimide (EDC, EOAC) at a final concentration of 2mM. Reactions were carried out at 4°C for 2 hours. Reactions were stopped by lowering the pH to 4 with 0.1 N acetic acid.

EXAMPLES 13

25 Multi-pegylated species

Modified MPOs having two or more PEGs (multi-pegylated) attached were also obtained from Examples 1-12 and were separated from the mono-pegylated using either anion or cation exchange chromatography.

EXAMPLE 14

Purification of Pegylated MPO

5 Pegylated MPO species were purified from the reaction mixture to >95% (SEC analysis) using either a single anion or cation exchange chromatography step (FIG 1).

While the present example shows the purification of 20K PEG-ALD MPO or 30K PEG-ALD MPO it is understood that similar purification methods could be used for other MPO molecules exemplified or disclosed herein.

Anion exchange chromatography

Anion exchange chromatography was carried out on a 5 mL Hitrap Q column (Pharmacia Biotech) equilibrated in 50 mM Tris pH 9.0 (Buffer A). The reaction mixture was diluted 5 fold with buffer A and loaded onto the column at a flow rate of 5 mL/min. Next, the column was washed with 5 column volumes of buffer A, followed by elution of the pegylated-MPO with a linear gradient of 0 to 20% buffer B (50 mM Tris pH 9.0, 1 M NaCl) in 20 column volumes. The eluant was monitored at 280 nm and 2 mL fractions were collected. Fractions containing monopegylated-MPO were pooled.

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Cation Exchange Chromatography

Cation exchange chromatography was carried out on an SP Sepharose high performance column (Pharmacia XK 26/20, 70 ml bed volume) equilibrated in 10 mM sodium acetate pH 4.5 (Buffer C). The reaction mixture was diluted 10X with buffer C and loaded onto the column at a flow rate of 5 mL/min. Next the column was washed with 5 column volumes of buffer C, followed by 5 column volumes of 12% buffer D (10 mM acetate pH 4.5, 1 M

NaCl). Subsequently, the PEG-MPO species were eluted from the column with a linear gradient of 12 to 27% buffer D in 20 column volumes. The eluant was monitored at 280 nm and 10 mL fractions were collected.

5 Fractions were pooled according to extent of pegylation (mono, di, tri etc.), exchanged into 10 mM acetate pH 4.5 buffer and concentrated to 1-5 mg/mL in a stirred cell fitted with an Amicon YM10 membrane. Protein concentration of pool was determined by A280 nm using an extinction coefficient of 0.71. Total yield of monopegylated MPO from this process was 10 to 50%.

EXAMPLE 15

15 Biochemical Characterization

The purified pegylated MPO pools were characterized by SDS-PAGE (FIG 2), Size Exclusion Chromatography (FIG 3a & 3b), RP HPLC (FIG 4), Tryptic mapping (FIG 5), and Sedimentation Analysis (Table 1).

SDS PAGE

SDS PAGE was carried out on 1 mm thick 12% reducing Novex Tris glycine gels and stained using a Novex Colloidal Coomassie TM G-250 staining kit (FIG 2).

Size Exclusion High Performance Liquid Chromatography (SEC-HPLC)

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Analytical SEC-HPLC was carried out using a Pharmacia Superdex 200 HR 10/30 column in 50 mM Tris pH 7.5, 150 mM NaCl at a flow rate of 0.4 mL/minute. PEG/protein elution was followed using a triple detector system

including UV monitor (220nm), differential refractometer (RI), and light scattering (LS) detector. FIG 3a shows a single peak corresponding to N-terminally monopegylated MPO and a single peak corresponding to MPO.

N-terminal Sequence and Peptide Mapping

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Following purification, Pegylated MPO(ie. 20K PEG-ALD MPO or 30K PEG-ALD MPO) was buffer-exchanged into a 10 dilution buffer comprised of 10mM Tris, pH 7.5/1X Modified Dulbecco's phosphate-buffered saline (MD-PBS) to a concentration of >2mg/ml using centrifugal concentration (Microsep™ Filtron, 10K Fast-Flux). N-15 terminal sequence analysis was determined (PE-Biosystems Model 494 Procise) and sample aliquots were digested overnight at 37°C using trypsin (Promega, V511C, from porcine) at 1:50 E:S. Digestions were quenched with 1M HCl and tryptic maps were then effected using a Vydac C-18 column eluted at 1.0ml/min 20 flow-rate using an acetonitrile gradient of ~0.33%/minute in 0.1% TFA. N-terminal sequence analysis and MALDI-TOF MS (PerSeptive Biosystems Voyager-DETMRP BioSpectrometry Workstation) were used to identify the disulfide-linked N-terminal fragment(s) in 25 the tryptic profile of control MPO.

N-terminal sequence analysis for both 20K PEG-ALD MPO and 30K PEG-ALD MPO revealed N-terminal heterogeneity, suggesting the presence of a combination of free N-terminal alanine as well as preview sequence coming from the N-alkylated (PEGylated) sample component. Differences in relative Edman degradation efficiency for free protein versus alkylated proteins, however,

preclude absolute quantitation. As such, tryptic map profiling (FIG 5) was utilized to indicate that ~90% of the pegylated MPO (both 20,000 and 30,000 PEG-ALD MPO species) was pegylated on the α -NH₂ group of the Nterminal alanine residue when judged by the relative decrease in intensity of the N-terminal disulfidelinked peptide(s) (peak between 105 and 120) compared to a tryptic map of control MPO. Since HPLC-SEC data had previously indicated that both pegylated-MPO species were quantitatively pegylated, it is likely that the other 10% of the pegylated MPO samples are pegylated elsewhere in the molecule, i.e. most likely on one or more of the E-NH2 groups of internal lysine residues, noting that there were only subtle differences observed for the other, non-N-terminal peaks in the fingerprint(s) as developed. MALDI-MS and N-terminal sequence analysis were used to positively identify the N-terminal fragment(s) in the map of control MPO, but were somewhat less definitive as tools for the identification of the more hydrophobic difference peaks eluting from the maps of the PEGylated MPO samples presumably due to the complex nature of these fragments.

25 Reversed Phase HPLC (RP HPLC)

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RP HPLC was carried out on a Phenomenex Jupiter C_{18} column (4.6 X 250 mm, 5 μ m particle size) at a temperature of 50°C. Samples were loaded onto the column equilibrated in 40% acetonitrile, 0.1% TFA at 1 mL/min. The column was washed with 3 mL 58% acetonitrile. Subsequently, the protein was eluted with a gradient from 58 to 63% acetonitrile over 27 minutes. The

monopegylated MPO species eluted as a single peak (FIG 4).

Sedimentation analysis

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The hydrodynamic radii of the two PEGylated MPO molecules (20K PEG-ALD MPO and the 30K PEG-ALD MPO) were determined using analytical ultracentrifugation technology. In sedimentation velocity experiments, one can measure the sedimentation coefficient "s" and the diffusional coefficient "D". From D, one can calculate the hydrodynamic radius (Rh) using the Stokes-Einstein Equation. Using the s/D ratio, one can calculate the molecular weight. TABLE 1 shows data from sedimentation velocity experiments carried out on MPO, N-terminally mono-PEGylated 20,000 MW PEG MPO, and N-terminally mono-PEGylated 30,000 MW PEG MPO.

TABLE 1
Sedimentation Velocity Results

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Hydrodynamic Radii and Molecular Weights Experimental MW based on Experimental Theoret. Sample Experimental S AA sequence $\mathbf{R}_{\mathbf{h}}$ R_h $\mathbf{M}_{\mathbf{w}}$ (from s/D Svedberg D and PEG size ratio) (Daltons) $10^{-7} \text{ cm}^2/\text{s}$ MPO 2.293 6.16 35,300 34,800 34.2 33.7 20 K PEG-ALD 1.774 3.52 55,650 54,800 59.9 59.0 MPO 1.628 2.52 72.6 30 K 74,610 64,800 83.6 PEG-ALD MPO

EXAMPLE 16

BAF 3/G-CSFR Cell proliferation assay

Mouse BaF 3 cell line transfected with genes encoding the human G-CSF (mBaF 3/hG-CSFR) receptor were used to examine hG-CSF agonist activity. mBaF3/hG-CSFR cells were seeded at 2.5 X 104 cells/well in 96 well microtiter plates containing serial dilution of cytokines. Cells were pulsed at T₅₆ hours with [methyl-10 ³H]-thymidine at 0.5 mCi per well for 18 hours. Plates were harvested onto glass fiber filter mats, and the incorporated radioactivity was measured by scintillation spectroscopy. The assay medium for the 15 cell lines consisted of IMDM supplemented with bovine serum albumin (BSA, 500 µg/ml, Boehringer Mannheim), human transferrin (100 μg/ml, Sigma), a lipid substitute consisting of 2.5 mg of phosphatidyl choline/ml of BSA and 50 mM 2-mercaptoethanol. Nterminally pegylated MPO was active in this assay. 20 TABLE 2 compares the in vitro IL-3 receptor and G-CSF receptor agonist bioactivities of mono and di- PEG-MPO species with un-PEGylated MPO.

TABLE 2

		Relative Potency		
5	MPO species	<u>AML</u>	<u>TF-1</u>	BAF3/G-CSFR
	MPO	1.0	1.0	1.0
	PEG-ALD			
	5K PEG MPO	0.124	0.144	0.775
10	20K PEG MPO	0.088	0.113	0.955
	30K PEG MPO	0.133	0.149	0.870
	di5K PEG MPO	0.093	0.105	1.509
	di30K PEG MPO	0.051	0.092	1.502
15	PEG-NHS			
	20K PEG MPO	0.268	0.600	1.696
	di20K PEG MPO	0.123	0.278	3.192
	tetra5K PEG MPO	0.086	0.090	4.216
	tetra5K NHS-SS PEG MPO	0.179	0.226	3.962
20	10K-Branch PEG MPO	0.297	0.632	0.980
	20K-Branch PEG MPO	0.281	0.550	1.505
	40K-Branch PEG MPO	0.337	0.613	1.654
	di10K-Branch PEG MPO	0.097	0.147	1.105
25	PEG-BTC			
	20K PEG MPO	0.321	0.925	4.686
	PEG-Hydrazide			
	20K PEG MPO	0.149	0.250	1.717
30	di20K PEG MPO	0.129	0.165	1.757
		•		

EXAMPLE 17

TF-1 proliferation assay

Human TF-1 cells, which express the hIL3 receptor were 5 used to identify hIL-3 receptor agonist activity. Human TF-1 cells were seeded at 1.25 X 104 cells/well in 96 well microtiter plates containing serial dilutions of cytokines. Cells were pulsed at T_{72} hours with [methyl-10 ³H]-thymidine at 0.5 mCi per well for 6 hours. Plates were harvested onto glass fiber filter mats, and the incorporated radioactivity was measured by scintillation spectroscopy. The assay medium for the cell lines consisted of IMDM supplemented with bovine serum albumin (BSA, 500 μ g/ml, Boehringer Mannheim), 15 human transferrin (100 μg/ml, Sigma), a lipid substitute consisting of 2.5 μ g of phosphatidyl choline/ml of BSA and 50 mM 2-mercaptoethanol. Nterminally pegylated MPO was active in this assay. 20 TABLE 2 compares the in vitro IL-3 receptor and G-CSF receptor agonist bioactivities of assorted PEG-MPO species with un-PEGylated MPO.

EXAMPLE 18

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AML proliferation assay

Human AML cells, which express the hIL3 and hG-CSF receptors were also used to measure MPO in vitro receptor agonist activity. Human AML cells were seeded at 2.5×10^4 cells/well in 96 well microtiter plates containing a serial dilution of cytokines. Cells were pulsed at T_{72} hours with [methyl- 3 H]-thymidine at 0.5 mCi per well for 24 hours. Plates were harvested onto

glass fiber filter mats, and the incorporated radioactivity was measured by scintillation spectroscopy. The assay medium for the cell lines consisted of IMDM supplemented with bovine serum

5 albumin (BSA, 500 µg/ml, Boehringer Mannheim), human transferrin (100 µg/ml, Sigma), a lipid substitute consisting of 2.5 µg of phosphatidyl choline/ml of BSA and 50 mM 2-mercaptoethanol. N-terminally pegylated MPO was active in this assay. TABLE 2 compares the in vitro IL-3 receptor and G-CSF receptor agonist bioactivities of assorted PEG-MPO species with un-PEGylated MPO.

EXAMPLE 19

15 CD34⁺ cell proliferation assays

Further assessment of the in vitro biological activity of N-terminally pegylated MPO (PEG-ALD MPO) was carried out in bone marrow CD34 cell proliferation bioassays. Fresh bone marrow aspirates were obtained through a 20 collaboration with the St. Louis University Medical School. Mononuclear cell fractions were recovered following density gradient centrifugation with Ficoll-Hypaque. CD34⁺ (stem and progenitor) cells were subsequently isolated by positive selection using the 25 Isolex 50 stem cell reagent kit (Baxter Healthcare Corporation, Deerfield, IL). This procedure yields an enriched cellular product where >90% of the cells express the CD34+ cell surface antigen. For proliferation assays, the CD34⁺ cells were incubated 30 overnight at 4°C in X-VIVO 10 media supplemented with 1% Human Serum Albumin. Following this incubation, the cells were washed, resuspended in X-VIVO 10 with 1% HSA, counted for viability and plated at 1 X 103

cells/well in 96 well microtiter plates containing a serial dilution of cytokines. Concentrations of the respective receptor agonists in co-addition experiments were equimolar at the indicated concentration value.

After 6 days, cells were pulsed with [methyl-3H]thymidine at 0.5 mCi per well for 7 hr, harvested onto
glass fiber filter mats, and the incorporated
radioactivity was measured by scintillation
spectroscopy. The N-terminally pegylated MPO yielded
proliferative responses slightly less than unmodified
MPO yet greater or equal to the responses from coadministration of IL-3 and G-CSF.

EXAMPLE 20

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CFU-GM clonogenic assays

Expansion of hematopoietic progenitors was demonstrated using human bone marrow-derived CD34+ cells in a colony forming unit granulocyte/macrophage (CFU-GM) assay, where clonogenic progenitors divide and differentiate in a semi-solid media in response to growth factors. CD34+ cells (isolated as described in example 19) were seeded in 35 mm tissue culture plates (10,000 cells/dish) in MethoCult H4230 (StemCell Technologies, Vancouver, BC) containing 0.9% Methylcellulose in IMDM, 30% FBS, 1% BSA, 1x10-4M 2-mercaptoethanol and 2mM L-glutamine.

Cultures were incubated with growth factors for 10-12 days at 37°C in humidified air containing 5% CO₂. The concentrations of the respective receptor agonists in co-addition experiments are equimolar each at the indicated concentration value. Hematopoietic colonies (>50 cells) were counted using an inverted microscope.

FIG 6 shows that the unmodified MPO molecule induces differentiation and expansion of hematopoietic progenitor cells into colony forming unit granulocyte/macrophage cells (CFU-GM) greater or equal to the responses from co-administration of hIL-3 and G-CSF.

Example 21

10 Normal Rhesus Monkey studies

The pharmacology of N-terminally pegylated MPO was assessed in normal Rhesus monkey (Macaca mulatta) studies. Rhesus monkeys (~5 Kg) were acclimated for 2 weeks during which the baseline blood data were 15 collected. Monkeys were given a single dose of PEG-MPO or control MPO by subcutaneous (SC), or intravenous (IV) injection. Monkeys were observed for clinical pharmacokinetics (PK) and pharmacodynamics (PD) 20 parameters up to 50 days post dosing. Blood samples were taken at regular intervals and hematological analyses were performed. Samples were dosed SC at 20 and 200 mg/kg. IV dosing studies were carried out at 10 mg/kg. Blood samples were taken at regular intervals 25 and hematological analyses were performed. Plasma samples were collected before dosing and at 0.5, 1, 2, 4, 6, 8, 14, 23.5, 47.5, 71.5, and 95.5 hr. after dosing.

30 Example 22

Normal Rhesus Pharmacokinetics

MPO protein concentration levels in rhesus plasma for PK analysis were determined using a sandwich ELISA. 96-well microtiter plates were coated with 150-mL/well affinity-purified goat-anti-G-CSF polyclonal diluted to 1mg/mL in 100 mM NaHCO₃, pH 8.2. Plates were incubated overnight at room temperature in a humidified chamber and blocked for one hour at 37°C with phosphate buffered saline, containing 3% bovine serum albumin (BSA) and 0.05% Poly(oxyethylene)-Sorbitan Monolaurate (Tween 20), pH 7.4. Plates were washed four times with 10 150 mM NaCl containing 0.05% Tween 20 (wash buffer). Plasma PK samples were initially diluted in assay buffer (PBS, 0.1% BSA, 0.01% Tween 20 pH 7.4), added to the plate and serially dlited 1:2 in an assay matrix of untreated Rhesus pooled plasma. The plasma 15 concentration of the matrix and the samples were matched by percentage. Plates were incubated for 2.5 hours at 37°C in a humidified chamber, then washed 4 times. Wells were washed four times. Affinity purified goat-anti-hIL3 receptor agonist polyclonal 20 antibody was diluted 1:5000 in assay buffer and 150 mg/mL well were added to each plate. Plates were incubated for 1.5 hours at 37°C in a humidified chamber. Wells were emptied and each well was again washed four times with wash buffer. Each well then 25 received 150 mL of TMB peroxidase substrate solution. Plates were incubated at room temperature for 10 minutes and read at a test wavelength of 650 nm on a microtiter plate reader (Molecular Devices 30 Corporation). Concentrations of immuno-reactive MPO in unknown PK samples were calculated from a standard curve using a four-parameter curve-fitting program supplied by Molecular Devices. Plasma concentration data and pharmacokinetic parameters, which were derived

from non-compartmental analysis, are shown in TABLE 3. The results indicate that the plasma residence time of the N-terminally pegylated MPO is greatly protracted when compared to the unmodified MPO. Pegylation 5 dramatically increases the drug exposure as AUC increases ~7-9 fold and ~10-20 fold for 20K and 30K PEG-MPO, respectively, compared to the unmodified MPO; and clearance rates decreased by up to 10 and 20 fold for 20K and 30K MPO, respectively, at the higher dose tested. MPO exposure increases in greater-than-10 proportional manner with dose, which indicates a nonlinear PK saturation of some "early" clearance mechanism. The IV profile suggests multi-phasic elimination distribution into a "deeper" compartment. Absolute bioavailability of PEG-MPO appears to be

15 Absolute bioavailability of PEG-MPO appears to be approximately 50% (data not shown).

TABLE 3 compares the *in vivo* pharmacokinetics of un-PEGylated and N-terminally mono-PEGylated 20,000 MW and 30,000 MW PEG-ALD MPO after a single subcutaneous dose in normal Rhesus monkeys.

TABLE 3 Plasma Concentration Data and Pharmacokinetic Parameters following a single subcutaneous dose of MPO, 20,000 MW OR 30,000 PEG-ALD MPO

Time (hr) Post-		20,000	30,000		20,000	30,000	r
dose	MPO	20,000 MW	30,000 MW	MPO	20,000 MW	30,000 MW	}
4000	20	PEG-	PEG-	200	PEG-	PEG-	l
		ALD	ALD	•	ALD	ALD	ŀ
	μg/kg	MPO	MPO	μg/kg	MPO	MPO	1
					200	200	1
		20 μg/kg	20 μg/kg			1	
0	O ^a	0.44	0	0	μg/kg 0.61	μg/kg 0	
0.5	1.00	11.0	1.60	110	134	168	
	2.90						
1		19.8	6.90	227	254	372	
2	5.90	44.3	22.7	298	540	686	
4	13.6	49.2	57.8	365	480	1530	
6	9.45	42.1	70.1	404	700	1670	
8	4.45	32.5	60.9	285	791	1980	<u> </u>
14	1.05	11.9	16.6	140	841	1870	
23.5	0.20	5.93	10.9	17.6	851	1710	
47.5	0	1.03	1.90	0	282	916	
71.5	NS	0	0.35	0	9.10	6.48	
95.5	NS	0	0	NS	2.75	2.31	
119.5	NS	NS	NS	NS	0	0	
Pharmacokinetic							units
Paramaters ^b							
C_{max}	13.6	49.2	70.1	425	955	2040	ng/mL
T_{max}	4	4	6	4.00	15.8	11	hr
AUC (0-24 hr)	84.6	520	725	3770	17600	38300	nG-
			Λ				hr/mL
AUC all	86.9	616	904	3900	34400	81100	nG-
							hr/mL
t _{last}	23.5	35.5	59.5	18.8	83.5	95.5	hr
T _{1/2}	3.23	9.02	10.1	3.8	8.08	7.81	hr
AUC (I)	85.3	610	905	3820	34400	81100	nG-
							hr/mL
CL/F	234	48.2	22.1	52.5	5.83	2.47	mL/hr-
							kg
V _d /F	1090	561	323	285	67.5	27.7	mL/kg
a na protein/ml pla							

⁵ a ng protein/mL plasma (n=2)

NS - no sample

 C_{max} – maximum concentration in plasma T_{max} – time at which C_{max} is achieved

10 AUC (0-24 hr) - Area under the curve from 0 to 24 hours

AUC all - total area under the curve

AUC (I) - AUC infinity

T_{last} - final time point at which sample is detected

 $T_{1/2}$ – terminal half life

15 CL - clearance rate

F-Bioavailability-fraction of dose reaching systemic circulation $V_d-volume$ distribution

^b Pharmacokinetic parameters derived from one compartmental analysis

EXAMPLE 23

Normal Rhesus Pharmacodynamics

Normal rhesus plasma samples were also analyzed for MPO · 5 pharmacological responses. Leukocytes were counted in a Technicon H1E Hematology Analyzer (Technicon Instruments Corp.). FIG 7 shows profiles for absolute neutrophil count (ANC) following SC dosing at 200 µg/kg as described above. A dramatic protraction in the WBC 10 and ANC response is observed with pegylated MPO. Also observed was a nearly identical 5-fold increase in WBC counts (C_{max}) after a single SC administration of either MPO or pegylated MPO (PEG-ALD MPO) at 200 µg/kg to 15 normal rhesus monkeys was driven by a 8-fold increase in neutrophil numbers within 8 hrs. Elevated total WBC and ANC levels returned to pretreatment levels within 3 or 4 days after dosing with MPO at 200 µg/kg. Both the 20,000 PEG MPO and 30,000 MW pegylated MPO maintained 20 elevated levels for over 160 hours with the latter yielding a remarkable increase (~6 fold) in total ANC at 80-100 hours compared to unmodified MPO. These data show good correlation with increases in the pharmacokinetic profile described above.

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EXAMPLE 27

Myelosuppressed rhesus (efficacy) studies

Male rhesus monkeys were housed in individual stainless steel cages in conventional holding rooms in animal facilities accredited by the American Association for Accreditation of Laboratory Care. Following a prehabituation period, monkeys were unilaterally

irradiated in Lucite restraining chairs with 250 kVp xradiation at 13 cGy/min in the post-anterior position, rotated 180° at the mid-dose (300 cGy) to the anteriorposterior position for completion of the total 600 cGy midline tissue exposure and randomly assigned to a 5 treatment protocol utilizing pegylated MPO or control autologous serum (AS). Pegylated MPO (30K PEG-ALD MPO) was subcutaneously administered according to the following two protocols: a) as two doses [200 μ g/kg, n=4] given one day and seven days following TBI, b) as 10 two doses [200 μ g/kg, n=4] given one day and four days following TBI, or c) as a single dose (600 μ g/kg, n=5) given one day following TBI. The irradiation controls (n=7) received 0.1% autologous serum (AS), daily for 18 days. Complete blood counts were monitored for up to 15 70 days following irradiation and the durations of neutropenia [absolute neutrophil count (ANC) < $500/\mu$ L] and thrombocytopenia (platelets (PLT) < 20,000/ μ L) were assessed. All animals received clinical support, which 20 consisted of antibiotics, fresh irradiated whole blood, and fluids as needed. An antibiotic regimen was initiated prophylactically when the white blood cell count (WBC) was $<1000/\mu$ L and continued daily until the WBC was $>1000/\mu$ L for three consecutive days. Fresh, irradiated (1500 cGy Co-60) whole blood (approximately 25 30 mLs/transfusion) from a random donor pool was administered when the PLT count was $< 20,000/\mu L$ and the hematocrit was <18%. Hematologic evaluations were determined using peripheral blood drawn from the saphenous vein in order to assay complete blood (Sysmex 30 K-4500) and differential counts (Wright-Giemsa Stain). TABLE 4 shows the efficacy of N-terminally mono-PEGylated 30,000 MW PEG MPO in a Rhesus monkey model of myelosuppression. Clinically relevant indicators such

as days where ANC's fell below 500/ml , ANC nadir, days to recovery, and days on antibiotics were measured for N-terminally mono-pegylated MPO using three dosing schedules.

One or more Key indicators in this model for clinical efficacy improve at all dosing schedules for pegylated MPO when compared to daily administration of un-Pegylated-MPO as a comparator.

TABLE 4

Treatment	ANC < 500 μl ⁻¹ (days)	ANC Nadir (μΙ ⁻¹)	Recovery (day)	Antibiotics (days)
0.1% AS (7)	14.8	8	20.8	16.8
MPO - QD (d1-18) 200μg/kg (n=4)	2.8	435	8.3	8.3
MPO - QOD (d1-17) 200µg/kg (n=8)	1.0	601	4.1	5.8
MPO - QD1 600µg/kg (n=4)	11.8	164	19.3	18.0
30K PEG-ALD MPO 200μg/kg d1,d4 (n=4)	3.0	244	8.8	6.8
30K PEG-ALD MPO 200μg/kg d1,d7 (n=4)	2.0	377	6.8	6.3
30K PEG-ALD MPO QD1 600μg/kg (n=5)	2.6	837	7.0	6.2

Treatment	PLT< 20000 μl ⁻¹ (days)	PLT Nadir (µl ⁻¹)	Recovery (day)	Number Transfusions
0.1% AS (7)	7.5	3,000	18.5	1.0
MPO - QD (d1-18)	4.0	20,500	12.0	0
$200\mu g/kg (n=4)$				
MPO - QOD (d1-17) 200μg/kg (n=8)	1.6	22,000	7.8	0
MPO - QD1 600μg/kg (n=4)	0.3	27,750	2.8	0
30K PEG-ALD MPO 200μg/kg d1,d4 (n=4)	1.0	21,500	7.3	0
30K PEG-ALD MPO 200μg/kg d1,d7 (n=4)	0.3	22,250	6.8	0
30K PEG-ALD MPO QD1 600μg/kg (n=5)	0.6	28,400	5.8	0.2

Example 28

Normal Rat Pharmacokinetics and Pharmacodynamics(PK/PD)

5 The pharmacokinetic and pharmacodynamic properties of PEGylated MPO molecules were assessed in normal rats. Male Sprague Dawley rats in groups of 5 were given a single subcutaneous injection of PEGylated MPO or control MPO at 500ug/kg. Blood samples were taken at regular intervals and analyzed for plasma protein concentrations and pharmacological responses as described in Examples 22 and 23.

TABLE 5

PK

PD

			AUC (Neutrophils hours /nL plasma)	
	24hr	48hr	72hr	
30K PEG ALD MPO	634	326	13	2026
20K PEG ALD MPO	468	242	1	2299
5K PEG ALD MPO	503	2	0	1866
di5K PEG ALD MPO	970	158	7	2156
40K Branch PEG2-NHS MPO	1539	518	19	2268
20K Branch PEG2-NHS MPO	301	72	7	2093
20K PEG-SPA MPO	711	139	2	1761
di20K PEG – SPA MPO	735	360	33	2329
10K Branch PEG NHS MPO	982	157	0	1384
di10K Branch PEG2-NHS MPO	945	247	10	1490
tetra 20K PEG- BTC MPO	572	192	10	2316
20K PEG-HZ MPO	2155	709	91	2569
di20K PEG-HZ MPO	499	289	47	3010
tetra5K PEG-SS MPO	881	40	0	1838
tetra5K PEG- SPA MPO	710	137	11	2272
di30K PEG- ALD MPO	504	193	28	2275
MPO	14	1	0	693

WHAT IS CLAIMED IS:

A Myelopoietin conjugate having at least one water-soluble polymer molecule covalently attached to at
 least one amino acid residue of a biologically active Myelopoietin polypeptide.

2. The Myelopoietin conjugate of claim 1 wherein said Myelopoietin polypeptide comprises a sequence of the formula selected from the group consisting of;

 R_1-L-R_2 , R_2-L-R_1 , R_1-R_2 , R_2-L-R_1 , $Met-Ala-R_1-L-R_2$, $Met-Ala-R_2-L-R_1$, $Met-Ala-R_1-R_2$, $Met-Ala-R_2-R_1$, $Met-R_1-L-R_2$, $Met-R_2-L-R_1$, $Met-R_1-R_2$, $Met-R_2-R_1$, $Ala-R_1-R_2$, $Ala-R_2-L-R_1$, $Ala-R_1-R_2$ and $Ala-R_2-R_1$;

wherein R₁ is a modified human interleukin-3 (hIL-3) amino acid sequence of SEQ ID NO:1;

20 wherein

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Xaa at position 17 is Ser, Lys, Gly, Asp, Met, Gln, or Arg; Xaa at position 18 is Asn, His, Leu, Ile, Phe, Arg, or Gln; Xaa at position 19 is Met, Phe, Ile, Arg, Gly, Ala, or Cys; Xaa at position 20 is Ile, Cys, Gln, Glu, Arg, Pro, or Ala;

25 Xaa at position 21 is Asp, Phe, Lys, Arg, Ala, Gly, Glu, Gln, Asn, Thr, Ser or Val;

Xaa at position 23 is Ile, Val, Ala, Leu, Gly, Trp, Lys,

30 Phe, Ser, or Arg;

Xaa at position 24 is Ile, Gly, Val, Arg, Ser, Phe, or Leu;

Xaa at position 25 is Thr, His, Gly, Gln, Arg, Pro, or Ala;

Xaa at position 26 is His, Thr, Phe, Gly, Arg, Ala, or Trp;

Xaa at position 27 is Leu, Gly, Arg, Thr, Ser, or Ala;

35 Xaa at position 28 is Lys, Arg, Leu, Gln, Gly, Pro, Val or Trp;

Xaa at position 29 is Gln, Asn, Leu, Pro, Arg, or Val;

Xaa at position 30 is Pro, His, Thr, Gly, Asp, Gln, Ser,

Leu, or Lys;

Xaa at position 31 is Pro, Asp, Gly, Ala, Arg, Leu, or Gln;

Xaa at position 32 is Leu, Val, Arg, Gln, Asn, Gly, Ala, or Glu;

Xaa at position 33 is Pro, Leu, Gln, Ala, Thr, or Glu;

- 5 Xaa at position 34 is Leu, Val, Gly, Ser, Lys, Glu, Gln, Thr, Arg, Ala, Phe, Ile or Met;
 - Xaa at position 35 is Leu, Ala, Gly, Asn, Pro, Gln, or Val;
 - Xaa at position 36 is Asp, Leu, or Val;
 - Xaa at position 37 is Phe, Ser, Pro, Trp, or Ile;
- 10 Xaa at position 38 is Asn, or Ala;
 - Xaa at position 40 is Leu, Trp, or Arg;
 - Xaa at position 41 is Asn, Cys, Arg, Leu, His, Met, or Pro;
 - Xaa at position 42 is Gly, Asp, Ser, Cys, Asn, Lys, Thr,
 - Leu, Val, Glu, Phe, Tyr, Ile, Met or Ala;
- 15 Xaa at position 43 is Glu, Asn, Tyr, Leu, Phe, Asp, Ala, Cys, Gln, Arg, Thr, Gly or Ser;
 - Xaa at position 44 is Asp, Ser, Leu, Arg, Lys, Thr, Met, Trp, Glu, Asn, Gln, Ala or Pro;
 - Xaa at position 45 is Gln, Pro, Phe, Val, Met, Leu, Thr,
- 20 Lys, Trp, Asp, Asn, Arg, Ser, Ala, Ile, Glu or His;
 - Xaa at position 46 is Asp, Phe, Ser, Thr, Cys, Glu, Asn,
 - Gln, Lys, His, Ala, Tyr, Ile, Val or Gly;
 - Xaa at position 47 is Ile, Gly, Val, Ser, Arg, Pro, or His;
 - Xaa at position 48 is Leu, Ser, Cys, Arg, Ile, His, Phe,
- 25 Glu, Lys, Thr, Ala, Met, Val or Asn;
 - Xaa at position 49 is Met, Arg, Ala, Gly, Pro, Asn, His, or Asp;
 - Xaa at position 50 is Glu, Leu, Thr, Asp, Tyr, Lys, Asn,
 - Ser, Ala, Ile, Val, His, Phe, Met or Gln;
 - Xaa at position 51 is Asn, Arg, Met, Pro, Ser, Thr, or His;
- 30 Xaa at position 52 is Asn, His, Arg, Leu, Gly, Ser, or Thr;
 - Xaa at position 53 is Leu, Thr, Ala, Gly, Glu, Pro, Lys, Ser, or Met;
 - Xaa at position 54 is Arg, Asp, Ile, Ser, Val, Thr, Gln,
 Asn, Lys, His, Ala or Leu;
- 35 Xaa at position 55 is Arg, Thr, Val, Ser, Leu, or Gly; Xaa at position 56 is Pro, Gly, Cys, Ser, Gln, Glu, Arg,

His, Thr, Ala, Tyr, Phe, Leu, Val or Lys;

```
Xaa at position 57 is Asn or Gly;
    Xaa at position 58 is Leu, Ser, Asp, Arg, Gln, Val, or Cys;
    Xaa at position 59 is Glu, Tyr, His, Leu, Pro, or Arg;
    Xaa at position 60 is Ala, Ser, Pro, Tyr, Asn, or Thr;
 5
    Xaa at position 61 is Phe, Asn, Glu, Pro, Lys, Arg, or Ser;
     Xaa at position 62 is Asn, His, Val, Arg, Pro, Thr, Asp, or Ile;
     Xaa at position 63 is Arg, Tyr, Trp, Lys, Ser, His, Pro, or Val;
    Xaa at position 64 is Ala, Asn, Pro, Ser, or Lys;
     Xaa at position 65 is Val, Thr, Pro, His, Leu, Phe, or Ser;
10
    Xaa at position 66 is Lys, Ile, Arg, Val, Asn, Glu, or Ser;
     Xaa at position 67 is Ser, Ala, Phe, Val, Gly, Asn, Ile,
           Pro, or His;
     Xaa at position 68 is Leu, Val, Trp, Ser, Ile, Phe, Thr, or His;
    Xaa at position 69 is Gln, Ala, Pro, Thr, Glu, Arg, Trp,
15
           Gly, or Leu;
     Xaa at position 70 is Asn, Leu, Val, Trp, Pro, or Ala;
     Xaa at position 71 is Ala, Met, Leu, Pro, Arg, Glu, Thr,
           Gln, Trp, or Asn;
     Xaa at position 72 is Ser, Glu, Met, Ala, His, Asn, Arg, or Asp;
20
    Xaa at position 73 is Ala, Glu, Asp, Leu, Ser, Gly, Thr, or Arg;
     Xaa at position 74 is Ile, Met, Thr, Pro, Arg, Gly, Ala;
    Xaa at position 75 is Glu, Lys, Gly, Asp, Pro, Trp, Arg,
           Ser, Gln, or Leu;
     Xaa at position 76 is Ser, Val, Ala, Asn, Trp, Glu, Pro,
25
           Gly, or Asp;
     Xaa at position 77 is Ile, Ser, Arg, Thr, or Leu;
    Xaa at position 78 is Leu, Ala, Ser, Glu, Phe, Gly, or Arg;
    Xaa at position 79 is Lys, Thr, Asn, Met, Arg, Ile, Gly, or Asp;
    Xaa at position 80 is Asn, Trp, Val, Gly, Thr, Leu, Glu, or Arg;
30
     Xaa at position 81 is Leu, Gln, Gly, Ala, Trp, Arg, Val, or Lys;
     Xaa at position 82 is Leu, Gln, Lys, Trp, Arg, Asp, Glu,
           Asn, His, Thr, Ser, Ala, Tyr, Phe, Ile, Met or Val;
    Xaa at position 83 is Pro, Ala, Thr, Trp, Arg, or Met;
    Xaa at position 84 is Cys, Glu, Gly, Arg, Met, or Val;
35
    Xaa at position 85 is Leu, Asn, Val, or Gln;
    Xaa at position 86 is Pro, Cys, Arg, Ala, or Lys;
    Xaa at position 87 is Leu, Ser, Trp, or Gly;
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Xaa at position 88 is Ala, Lys, Arg, Val, or Trp; Xaa at position 89 is Thr, Asp, Cys, Leu, Val, Glu, His, Asn, or Ser; Xaa at position 90 is Ala, Pro, Ser, Thr, Gly, Asp, Ile, or Met; Xaa at position 91 is Ala, Pro, Ser, Thr, Phe, Leu, Asp, or His; Xaa at position 92 is Pro, Phe, Arg, Ser, Lys, His, Ala, Gly, Ile or Leu; Xaa at position 93 is Thr, Asp, Ser, Asn, Pro, Ala, Leu, or Arg; Xaa at position 94 is Arg, Ile, Ser, Glu, Leu, Val, Gln, 10 Lys, His, Ala, or Pro; Xaa at position 95 is His, Gln, Pro, Arg, Val, Leu, Gly, Thr, Asn, Lys, Ser, Ala, Trp, Phe, Ile, or Tyr; Xaa at position 96 is Pro, Lys, Tyr, Gly, Ile, or Thr; Xaa at position 97 is Ile, Val, Lys, Ala, or Asn; 15 Xaa at position 98 is His, Ile, Asn, Leu, Asp, Ala, Thr, Glu, Gln, Ser, Phe, Met, Val, Lys, Arg, Tyr or Pro; Xaa at position 99 is Ile, Leu, Arg, Asp, Val, Pro, Gln, Gly, Ser, Phe, or His; Xaa at position 100 is Lys, Tyr, Leu, His, Arg, Ile, Ser, 20 Gln, or Pro; Xaa at position 101 is Asp; Xaa at position 102 is Gly, Leu, Glu, Lys, Ser, Tyr, or Pro; Xaa at position 103 is Asp, or Ser; Xaa at position 104 is Trp, Val, Cys, Tyr, Thr, Met, Pro, 25 Leu, Gln, Lys, Ala, Phe, or Gly; Xaa at position 105 is Asn, Pro, Ala, Phe, Ser, Trp, Gln, Tyr, Leu, Lys, Ile, Asp, or His; Xaa at position 106 is Glu, Ser, Ala, Lys, Thr, Ile, Gly, or Pro; Xaa at position 108 is Arg, Lys, Asp, Leu, Thr, Ile, Gln, 30 His, Ser, Ala or Pro; Xaa at position 109 is Arg, Thr, Pro, Glu, Tyr, Leu, Ser, or Gly; Xaa at position 110 is Lys, Ala, Asn, Thr, Leu, Arg, Gln, His, Glu, Ser, Ala, or Trp; Xaa at position 111 is Leu, Ile, Arg, Asp, or Met; 35 Xaa at position 112 is Thr, Val, Gln, Tyr, Glu, His, Ser, or Phe; Xaa at position 113 is Phe, Ser, Cys, His, Gly, Trp, Tyr, Asp, Lys, Leu, Ile, Val or Asn;

Xaa at position 114 is Tyr, Cys, His, Ser, Trp, Arg, or Leu;
Xaa at position 115 is Leu, Asn, Val, Pro, Arg, Ala, His,
 Thr, Trp, or Met;

Xaa at position 116 is Lys;

25

- Xaa at position 117 is Thr, Ser, Asn, Ile, Trp, Lys, or Pro;
 Xaa at position 118 is Leu, Ser, Pro, Ala, Glu, Cys, Asp, or Tyr;
 Xaa at position 119 is Glu, Ser, Lys, Pro, Leu, Thr, Tyr, or Arg;
 Xaa at position 120 is Asn, Ala, Pro, Leu, His, Val, or Gln;
 Xaa at position 121 is Ala, Ser, Ile, Asn, Pro, Lys, Asp, or Gly;
- 10 Xaa at position 122 is Gln, Ser, Met, Trp, Arg, Phe, Pro, His, Ile, Tyr, or Cys;

Xaa at position 123 is Ala, Met, Glu, His, Ser, Pro, Tyr, or Leu;

wherein from 1 to about 44 of the amino acids designated by Xaa are different from the corresponding amino acids of native (1-133) human interleukin-3; and wherein from 1 to 14 amino acids are optionally deleted from the N-terminus and/or from 1 to 15 amino acids are optionally deleted from the C-terminus of said sequence of SEQ ID NO:1;

 R_2 is a factor selected from the group consisting of: a colony stimulating factor, a cytokine, a lymphokine, an interleukin, and a hematopoietic growth factor; and

L is a linker capable of linking R1 to R2.

3. The Myelopoietin conjugate of claim 2 wherein in said Myelopoietin polypeptide said factor is selected from the group consisting of;

GM-CSF, G-CSF, G-CSF Ser¹⁷, c-mpl ligand (TPO),
MGDF, M-CSF, erythropoietin (EPO), IL-1, IL-4, IL-2, IL35 3, IL-5, IL 6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12,

IL-13, IL-15, LIF, flt3/flk2 ligand, and stem cell factor (SCF).

4. The Myelopoietin conjugate of claim 1 wherein in said biologically active Myelopoietin polypeptide R_1 is selected from the group consisting of:

SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID 10 NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, residues 2-113 of SEQ ID NO:25, residues 3-113 of SEQ ID NO:25, SEQ ID NO:26, residues 2-113 of SEQ ID NO:26, residues 3-113 of SEQ ID NO:26, SEQ ID NO:27, residues 2-113 of SEQ ID NO:27, residues 15 3-113 of SEQ ID NO:27, SEQ ID NO:28, residues 2-113 of SEQ ID NO:28, residues 3-113 of SEQ ID NO:28, SEQ ID NO:29, residues 2-113 of SEQ ID NO:29, residues 3-113 of SEO ID NO:29, SEO ID NO:30, residues 2-113 of SEO ID 20 NO:30, residues 3-113 of SEQ ID NO:30, SEQ ID NO:31, residues 2-113 of SEQ ID NO:31, residues 3-113 of SEQ ID NO:31, SEQ ID NO:32, residues 2-113 of SEQ ID NO:32, residues 3-113 of SEQ ID NO:32, SEQ ID NO:33, residues 2-113 of SEQ ID NO:33, residues 3-113 of SEQ ID NO:33, 25 SEQ ID NO:34, residues 2-113 of SEQ ID NO:34, residues 3-113 of SEQ ID NO:34, SEQ ID NO:35, residues 2-113 of SEQ ID NO:35, residues 3-113 of SEQ ID NO:35, SEQ ID NO:36, residues 2-113 of SEQ ID NO:36, residues 3-113 of SEQ ID NO:36, SEQ ID NO:37, residues 2-113 of SEQ ID 30 NO:37, residues 3-113 of SEQ ID NO:37, SEQ ID NO:38, residues 2-113 of SEQ ID NO:38, residues 3-113 of SEQ ID NO:38, SEQ ID NO:39, residues 2-113 of SEQ ID NO:39, residues 3-113 of SEQ ID NO:39, SEQ ID NO:40, residues 2-113 of SEQ ID NO:40, residues 3-113 of SEQ ID NO:41, 35 SEQ ID NO:42, SEQ ID NO:43, residues 2-113 of SEQ ID

NO:43, residues 3-113 of SEQ ID NO:43, SEQ ID NO:44, residues 2-113 of SEQ ID NO:45, residues 3-113 of SEQ ID NO:45, SEQ ID NO:48, residues 2-113 of SEQ ID NO:48, residues 3-113 of SEQ ID NO:48, SEQ ID NO:49, residues 2-113 of SEQ ID NO:49, residues 3-113 of SEQ ID NO:49, SEQ ID NO:53 through SEQ ID NO:120, residues 2-113 of SEQ ID NO:53 through SEQ ID NO:120, residues 3-113 of SEQ ID NO:53 through SEQ ID NO:120.

10 5. The Myelopoietin conjugate of claim 1 where said biologically active Myelopoietin polypeptide is selected from the group consisting of:

SEQ ID NO:121-124, 134, 135, 146, 147, 152, 158, 15 159, residues 2-307 of SEQ ID NO:121-124, 134, 135, 146, 147, 152, 158, 159, residues 3-307 of SEQ ID NO:121-124, 134, 135, 146, 147, 152, 158, 159, SEQ ID NO:125-127, 136, 153, residues 2-244 of SEO ID NO:125-127, 136, 153, residues 3-244 of SEQ ID NO:125-127, 136, 153, SEQ ID 20 NO:128-130, 138, 149, 150, 154, 156, 157, residues 2-322 of SEQ ID NO: 128-130, 138, 149, 150, 154, 156, 157, residues 3-322 of SEQ ID NO: 128-130, 138, 149, 150, 154, 156, 157, SEQ ID NO:131-133, 137, 141, 155, residues 2-259 of SEQ ID NO:131-133, 137, 141, 155, 25 residues 3-259 of SEQ ID NO:131-133, 137, 141, 155, SEO ID NO:139, 151, residues 2-349 of SEQ ID NO:139, 151, residues 3-349 of SEQ ID NO:139, 151, SEQ ID NO:141, residues 2-301 of SEQ ID NO:141, residues 3-301 of SEQ ID NO:141, SEQ ID NO:143, residues 2-335 of SEQ ID 30 NO:143, residues 3-335 of SEQ ID NO:143, SEQ ID NO:144, residues 2-274 of SEO ID NO:144, residues 3-274 of SEO ID NO:144, SEQ ID NO:145, residues 2-317 of SEQ ID NO:145, residues 3-317 of SEQ ID NO:145, SEQ ID NO:148, residues 2-337 of SEQ ID NO:148, residues 3-337 of SEQ 35 ID NO:148, SEQ ID NO:165-167, residues 2-286 of SEQ ID

NO:165-167, residues 3-286 of SEQ ID NO:165-167, SEQ ID NO:168, residues 2-290 of SEQ ID NO:168, residues 3-290 of SEQ ID NO:168, SEQ ID NO:178, SEQ ID NO:181, SEQ ID NO:184, SEQ ID NO:187, SEQ ID NO:190, SEQ ID NO:193, SEQ ID NO:196, SEQ ID NO:199, SEQ ID NO:202, SEQ ID NO:205, 5 SEQ ID NO:208, SEQ ID NO:211, SEQ ID NO:214, SEQ ID NO:217, SEQ ID NO:220, SEQ ID NO:223, SEQ ID NO:226, SEQ ID NO:229, SEQ ID NO:232, SEQ ID NO:235, SEQ ID NO:238, SEQ ID NO:241, SEQ ID NO:244, SEQ ID NO:247, SEQ ID 10 NO:250, SEQ ID NO:253, SEQ ID NO:256, SEQ ID NO:259, SEQ ID NO:262, SEQ ID NO:265, SEQ ID NO:268, SEQ ID NO:271, SEQ ID NO:274, SEQ ID NO:277, SEQ ID NO:280, SEQ ID NO:283, SEQ ID NO:286, SEQ ID NO:289, SEQ ID NO:292, SEQ ID NO:295, SEQ ID NO:298, SEQ ID NO:301, SEQ ID NO:304, SEQ ID NO:307, SEQ ID NO:310, SEQ ID NO:313, SEQ ID 15 NO:316, SEQ ID NO:319, SEQ ID NO:322, SEQ ID NO:325, SEQ ID NO:328, SEQ ID NO:331, SEQ ID NO:334, SEQ ID NO:337, SEQ ID NO:340, SEQ ID NO:343, SEQ ID NO:346, SEQ ID NO:349, SEQ ID NO:352, SEQ ID NO:355, SEQ ID NO:358, SEQ ID NO:361, SEQ ID NO:364, SEQ ID NO:367, SEQ ID NO:370, 20 SEQ ID NO:373, SEQ ID NO:376, SEQ ID NO:379, SEQ ID NO:382, residues 2-307 of SEQ ID NO:178, residues 2-307 of SEQ ID NO:181, residues 2-307 of SEQ ID NO:184, residues 2-307 of SEO ID NO:187, residues 2-307 of SEO ID NO:190, residues 2-307 of SEQ ID NO:193, residues 2-25 307 of SEQ ID NO:196, residues 2-307 of SEQ ID NO:199, residues 2-307 of SEQ ID NO:202, residues 2-307 of SEQ ID NO:205, residues 2-307 of SEQ ID NO:208, residues 2-307 of SEQ ID NO:211, residues 2-307 of SEQ ID NO:214, 30 residues 2-307 of SEQ ID NO:217, residues 2-307 of SEQ ID NO:220, residues 2-307 of SEQ ID NO:223, residues 2-307 of SEQ ID NO:226, residues 2-307 of SEQ ID NO:229, residues 2-307 of SEQ ID NO:232, residues 2-307 of SEQ ID NO:235, residues 2-307 of SEQ ID NO:238, residues 2-35 307 of SEQ ID NO:241, residues 2-307 of SEQ ID NO:244,

residues 2-307 of SEQ ID NO:247, residues 2-307 of SEQ ID NO:250, residues 2-307 of SEQ ID NO:253, residues 2-307 of SEQ ID NO:256, residues 2-307 of SEQ ID NO:259, residues 2-307 of SEQ ID NO:262, residues 2-307 of SEQ 5 ID NO:265, residues 2-307 of SEQ ID NO:268, residues 2-307 of SEQ ID NO:271, residues 2-307 of SEQ ID NO:274, residues 2-307 of SEQ ID NO:277, residues 2-307 of SEQ ID NO:280, residues 2-307 of SEQ ID NO:283, residues 2-307 of SEQ ID NO:286, residues 2-307 of SEQ ID NO:289, residues 2-307 of SEQ ID NO:292, residues 2-307 of SEQ 10 ID NO:295, residues 2-307 of SEQ ID NO:298, residues 2-307 of SEQ ID NO:301, residues 2-307 of SEQ ID NO:304, residues 2-307 of SEQ ID NO:307, residues 2-307 of SEQ ID NO:310, residues 2-307 of SEQ ID NO:313, residues 2-307 of SEQ ID NO:316, residues 2-307 of SEQ ID NO:319, 15 residues 2-307 of SEQ ID NO:322, residues 2-307 of SEQ ID NO:325, residues 2-307 of SEQ ID NO:328, residues 2-307 of SEQ ID NO:331, residues 2-307 of SEQ ID NO:334, residues 2-307 of SEQ ID NO:337, residues 2-307 of SEQ 20 ID NO:340, residues 2-307 of SEQ ID NO:343, residues 2-307 of SEQ ID NO:346, residues 2-307 of SEQ ID NO:349, residues 2-307 of SEQ ID NO:352, residues 2-307 of SEQ ID NO:355, residues 2-307 of SEQ ID NO:358, residues 2-307 of SEQ ID NO:361, residues 2-307 of SEQ ID NO:364, 25 residues 2-307 of SEQ ID NO:367, residues 2-307 of SEQ ID NO:370, residues 2-307 of SEQ ID NO:373, residues 2-307 of SEQ ID NO:376, residues 2-307 of SEQ ID NO:379, residues 2-307 of SEQ ID NO:382, residues 3-307 of SEQ ID NO:178, residues 3-307 of SEQ ID NO:181, residues 3-307 of SEQ ID NO:184, residues 3-307 of SEQ ID NO:187, 30 residues 3-307 of SEQ ID NO:190, residues 3-307 of SEQ ID NO:193, residues 3-307 of SEQ ID NO:196, residues 3-307 of SEQ ID NO:199, residues 3-307 of SEQ ID NO:202, residues 3-307 of SEQ ID NO:205, residues 3-307 of SEQ ID NO:208, residues 3-307 of SEQ ID NO:211, residues 3-35

307 of SEQ ID NO:214, residues 3-307 of SEQ ID NO:217, residues 3-307 of SEQ ID NO:220, residues 3-307 of SEQ ID NO:223, residues 3-307 of SEQ ID NO:226, residues 3-307 of SEQ ID NO:229, residues 3-307 of SEQ ID NO:232, 5 residues 3-307 of SEQ ID NO:235, residues 3-307 of SEQ ID NO:238, residues 3-307 of SEQ ID NO:241, residues 3-307 of SEQ ID NO:244, residues 3-307 of SEQ ID NO:247, residues 3-307 of SEQ ID NO:250, residues 3-307 of SEQ ID NO:253, residues 3-307 of SEQ ID NO:256, residues 3-307 of SEQ ID NO:259, residues 3-307 of SEQ ID NO:262, 10 residues 3-307 of SEQ ID NO:265, residues 3-307 of SEQ ID NO:268, residues 3-307 of SEQ ID NO:271, residues 3-307 of SEQ ID NO:274, residues 3-307 of SEQ ID NO:277, residues 3-307 of SEQ ID NO:280, residues 3-307 of SEQ 15 ID NO:283, residues 3-307 of SEQ ID NO:286, residues 3-307 of SEQ ID NO:289, residues 3-307 of SEQ ID NO:292, residues 3-307 of SEQ ID NO:295, residues 3-307 of SEQ ID NO:298, residues 3-307 of SEQ ID NO:301, residues 3-307 of SEQ ID NO:304, residues 3-307 of SEQ ID NO:307, residues 3-307 of SEQ ID NO:310, residues 3-307 of SEQ 20 ID NO:313, residues 3-307 of SEQ ID NO:316, residues 3-307 of SEQ ID NO:319, residues 3-307 of SEQ ID NO:322, residues 3-307 of SEQ ID NO:325, residues 3-307 of SEQ ID NO:328, residues 3-307 of SEO ID NO:331, residues 3-25 307 of SEQ ID NO:334, residues 3-307 of SEQ ID NO:337, residues 3-307 of SEQ ID NO:340, residues 3-307 of SEQ ID NO:343, residues 3-307 of SEQ ID NO:346, residues 3-307 of SEQ ID NO:349, residues 3-307 of SEQ ID NO:352, residues 3-307 of SEQ ID NO:355, residues 3-307 of SEQ 30 ID NO:358, residues 3-307 of SEQ ID NO:361, residues 3-307 of SEQ ID NO:364, residues 3-307 of SEQ ID NO:367, residues 3-307 of SEQ ID NO:370, residues 3-307 of SEQ ID NO:373, residues 3-307 of SEQ ID NO:376, residues 3-307 of SEQ ID NO:379, residues 3-307 of SEQ ID NO:382, 35 SEQ ID NO:179, SEQ ID NO:182, SEQ ID NO:185, SEQ ID

NO:188, SEQ ID NO:191, SEQ ID NO:194, SEQ ID NO:197, SEQ ID NO:200, SEQ ID NO:203, SEO ID NO:206, SEO ID NO:209, SEQ ID NO:212, SEQ ID NO:215, SEQ ID NO:218, SEQ ID NO:221, SEQ ID NO:224, SEQ ID NO:227, SEQ ID NO:230, SEQ 5 ID NO:233, SEQ ID NO:236, SEO ID NO:239, SEO ID NO:242, SEQ ID NO:245, SEQ ID NO:248, SEQ ID NO:251, SEQ ID NO:254, SEQ ID NO:257, SEQ ID NO:260, SEQ ID NO:263, SEQ ID NO:266, SEQ ID NO:269, SEQ ID NO:272, SEQ ID NO:275, SEQ ID NO:278, SEQ ID NO:281, SEQ ID NO:284, SEQ ID 10 NO:287, SEQ ID NO:290, SEQ ID NO:293, SEQ ID NO:296, SEQ ID NO:299, SEQ ID NO:302, SEQ ID NO:305, SEQ ID NO:308, SEQ ID NO:311, SEQ ID NO:314, SEQ ID NO:317, SEQ ID NO:320, SEQ ID NO:323, SEQ ID NO:326, SEQ ID NO:329, SEQ ID NO:332, SEQ ID NO:335, SEQ ID NO:338, SEQ ID NO:341, 15 SEQ ID NO:344, SEQ ID NO:347, SEO ID NO:350, SEO ID NO:353, SEQ ID NO:356, SEQ ID NO:359, SEQ ID NO:362, SEQ ID NO:365, SEQ ID NO:368, SEQ ID NO:371, SEQ ID NO:374, SEQ ID NO:377, SEQ ID NO:380, SEQ ID NO:383, residues 2-322 of SEQ ID NO:179, residues 2-322 of SEQ ID NO:182, 20 residues 2-322 of SEQ ID NO:185, residues 2-322 of SEQ ID NO:188, residues 2-322 of SEQ ID NO:191, residues 2-322 of SEQ ID NO:194, residues 2-322 of SEQ ID NO:197, residues 2-322 of SEQ ID NO:200, residues 2-322 of SEQ ID NO:203, residues 2-322 of SEQ ID NO:206, residues 2-322 of SEQ ID NO: 209, residues 2-322 of SEQ ID NO: 212, 25 residues 2-322 of SEQ ID NO:215, residues 2-322 of SEQ ID NO:218, residues 2-322 of SEQ ID NO:221, residues 2-322 of SEQ ID NO:224, residues 2-322 of SEQ ID NO:227, residues 2-322 of SEQ ID NO:230, residues 2-322 of SEQ ID NO:233, residues 2-322 of SEQ ID NO:236, residues 2-30 322 of SEO ID NO:239, residues 2-322 of SEO ID NO:242, residues 2-322 of SEQ ID NO:245, residues 2-322 of SEQ ID NO:248, residues 2-322 of SEQ ID NO:251, residues 2-322 of SEO ID NO:254, residues 2-322 of SEO ID NO:257, residues 2-322 of SEQ ID NO:260, residues 2-322 of SEQ 35

ID NO:263, residues 2-322 of SEQ ID NO:266, residues 2-322 of SEO ID NO:269, residues 2-322 of SEO ID NO:272, residues 2-322 of SEQ ID NO:275, residues 2-322 of SEQ ID NO:278, residues 2-322 of SEQ ID NO:281, residues 2-322 of SEO ID NO:284, residues 2-322 of SEO ID NO:287, 5 residues 2-322 of SEQ ID NO:290, residues 2-322 of SEQ ID NO:293, residues 2-322 of SEQ ID NO:296, residues 2-322 of SEQ ID NO:299, residues 2-322 of SEQ ID NO:302, residues 2-322 of SEQ ID NO:305, residues 2-322 of SEQ 10 ID NO:308, residues 2-322 of SEQ ID NO:311, residues 2-322 of SEO ID NO:314, residues 2-322 of SEO ID NO:317, residues 2-322 of SEQ ID NO:320, residues 2-322 of SEQ ID NO:323, residues 2-322 of SEQ ID NO:326, residues 2-322 of SEQ ID NO:329, residues 2-322 of SEQ ID NO:332, residues 2-322 of SEQ ID NO:335, residues 2-322 of SEQ 15 ID NO:338, residues 2-322 of SEQ ID NO:341, residues 2-322 of SEQ ID NO:344, residues 2-322 of SEQ ID NO:347, residues 2-322 of SEQ ID NO:350, residues 2-322 of SEQ ID NO:353, residues 2-322 of SEQ ID NO:356, residues 2-20 322 of SEQ ID NO:359, residues 2-322 of SEQ ID NO:362, residues 2-322 of SEQ ID NO:365, residues 2-322 of SEQ ID NO:368, residues 2-322 of SEQ ID NO:371, residues 2-322 of SEQ ID NO:374, residues 2-322 of SEQ ID NO:377, residues 2-322 of SEQ ID NO:380, residues 2-322 of SEQ 25 ID NO:383, residues 3-322 of SEQ ID NO:179, residues 3-322 of SEQ ID NO:182, residues 3-322 of SEQ ID NO:185, residues 3-322 of SEQ ID NO:188, residues 3-322 of SEQ ID NO:191, residues 3-322 of SEQ ID NO:194, residues 3-322 of SEQ ID NO:197, residues 3-322 of SEQ ID NO:200, residues 3-322 of SEQ ID NO:203, residues 3-322 of SEQ 30 ID NO:206, residues 3-322 of SEQ ID NO:209, residues 3-322 of SEQ ID NO:212, residues 3-322 of SEQ ID NO:215, residues 3-322 of SEQ ID NO:218, residues 3-322 of SEQ ID NO:221, residues 3-322 of SEQ ID NO:224, residues 3-322 of SEQ ID NO:227, residues 3-322 of SEQ ID NO:230, 35

residues 3-322 of SEQ ID NO:233, residues 3-322 of SEQ ID NO:236, residues 3-322 of SEQ ID NO:239, residues 3-322 of SEQ ID NO:242, residues 3-322 of SEQ ID NO:245, residues 3-322 of SEQ ID NO:248, residues 3-322 of SEQ 5 ID NO:251, residues 3-322 of SEQ ID NO:254, residues 3-322 of SEQ ID NO:257, residues 3-322 of SEQ ID NO:260, residues 3-322 of SEQ ID NO:263, residues 3-322 of SEQ ID NO:266, residues 3-322 of SEQ ID NO:269, residues 3-322 of SEQ ID NO:272, residues 3-322 of SEQ ID NO:275, residues 3-322 of SEQ ID NO:278, residues 3-322 of SEQ 10 ID NO:281, residues 3-322 of SEQ ID NO:284, residues 3-322 of SEQ ID NO:287, residues 3-322 of SEQ ID NO:290, residues 3-322 of SEQ ID NO:293, residues 3-322 of SEQ ID NO:296, residues 3-322 of SEQ ID NO:299, residues 3-15 322 of SEQ ID NO:302, residues 3-322 of SEQ ID NO:305, residues 3-322 of SEQ ID NO:308, residues 3-322 of SEQ ID NO:311, residues 3-322 of SEQ ID NO:314, residues 3-322 of SEQ ID NO:317, residues 3-322 of SEQ ID NO:320, residues 3-322 of SEQ ID NO:323, residues 3-322 of SEQ ID NO:326, residues 3-322 of SEQ ID NO:329, residues 3-20 322 of SEQ ID NO:332, residues 3-322 of SEQ ID NO:335, residues 3-322 of SEO ID NO:338, residues 3-322 of SEO ID NO:341, residues 3-322 of SEQ ID NO:344, residues 3-322 of SEQ ID NO:347, residues 3-322 of SEQ ID NO:350, 25 residues 3-322 of SEQ ID NO:353, residues 3-322 of SEQ ID NO:356, residues 3-322 of SEQ ID NO:359, residues 3-322 of SEQ ID NO:362, residues 3-322 of SEQ ID NO:365, residues 3-322 of SEQ ID NO:368, residues 3-322 of SEQ ID NO:371, residues 3-322 of SEQ ID NO:374, residues 3-30 322 of SEQ ID NO:377, residues 3-322 of SEQ ID NO:380, residues 3-322 of SEQ ID NO:383, SEQ ID NO:180, SEQ ID NO:183, SEQ ID NO:186, SEQ ID NO:189, SEQ ID NO:192, SEQ ID NO:195, SEQ ID NO:198, SEQ ID NO:201, SEQ ID NO:204, SEQ ID NO:207, SEQ ID NO:210, SEQ ID NO:213, SEQ ID NO:216, SEQ ID NO:219, SEQ ID NO:222, SEQ ID NO:225, SEQ 35

ID NO:228, SEQ ID NO:231, SEQ ID NO:234, SEQ ID NO:237, SEO ID NO:240, SEO ID NO:243, SEO ID NO:246, SEO ID NO:249, SEQ ID NO:252, SEQ ID NO:255, SEQ ID NO:258, SEQ ID NO:261, SEQ ID NO:264, SEQ ID NO:267, SEQ ID NO:270, 5 SEO ID NO:273, SEO ID NO:276, SEO ID NO:279, SEO ID NO:282, SEQ ID NO:285, SEQ ID NO:288, SEQ ID NO:291, SEQ ID NO:294, SEQ ID NO:297, SEQ ID NO:300, SEQ ID NO:303, SEQ ID NO:306, SEQ ID NO:309, SEQ ID NO:312, SEQ ID NO:315, SEQ ID NO:318, SEQ ID NO:321, SEQ ID NO:324, SEQ ID NO:327, SEQ ID NO:330, SEQ ID NO:333, SEQ ID NO:336, 10 SEO ID NO:339, SEO ID NO:342, SEO ID NO:345, SEO ID NO:348, SEQ ID NO:351, SEQ ID NO:354, SEQ ID NO:357, SEQ ID NO:360, SEQ ID NO:363, SEQ ID NO:366, SEQ ID NO:369, SEQ ID NO:372, SEQ ID NO:375, SEQ ID NO:378, SEQ ID 15 NO:381, SEQ ID NO:384, residues 2-349 of SEQ ID NO:179, residues 2-349 of SEQ ID NO:182, residues 2-349 of SEQ ID NO:185, residues 2-349 of SEQ ID NO:188, residues 2-349 of SEQ ID NO:191, residues 2-349 of SEQ ID NO:194, residues 2-349 of SEQ ID NO:197, residues 2-349 of SEQ 20 ID NO:200, residues 2-349 of SEQ ID NO:203, residues 2-349 of SEQ ID NO: 206, residues 2-349 of SEQ ID NO: 209, residues 2-349 of SEQ ID NO:212, residues 2-349 of SEQ ID NO:215, residues 2-349 of SEQ ID NO:218, residues 2-349 of SEQ ID NO: 221, residues 2-349 of SEQ ID NO: 224, residues 2-349 of SEQ ID NO:227, residues 2-349 of SEQ 25 ID NO:230, residues 2-349 of SEQ ID NO:233, residues 2-349 of SEQ ID NO:236, residues 2-349 of SEQ ID NO:239, residues 2-349 of SEQ ID NO:242, residues 2-349 of SEQ ID NO:245, residues 2-349 of SEQ ID NO:248, residues 2-349 of SEQ ID NO:251, residues 2-349 of SEQ ID NO:254, 30 residues 2-349 of SEQ ID NO:257, residues 2-349 of SEQ ID NO:260, residues 2-349 of SEQ ID NO:263, residues 2-349 of SEQ ID NO:266, residues 2-349 of SEQ ID NO:269, residues 2-349 of SEQ ID NO:272, residues 2-349 of SEQ ID NO:275, residues 2-349 of SEQ ID NO:278, residues 2-35

349 of SEQ ID NO:281, residues 2-349 of SEQ ID NO:284, residues 2-349 of SEQ ID NO:287, residues 2-349 of SEQ ID NO:290, residues 2-349 of SEQ ID NO:293, residues 2-349 of SEQ ID NO:296, residues 2-349 of SEQ ID NO:299, 5 residues 2-349 of SEQ ID NO:302, residues 2-349 of SEQ ID NO:305, residues 2-349 of SEQ ID NO:308, residues 2-349 of SEQ ID NO:311, residues 2-349 of SEQ ID NO:314, residues 2-349 of SEQ ID NO:317, residues 2-349 of SEQ ID NO:320, residues 2-349 of SEQ ID NO:323, residues 2-349 of SEQ ID NO:326, residues 2-349 of SEQ ID NO:329, 10 residues 2-349 of SEQ ID NO:332, residues 2-349 of SEQ ID NO:335, residues 2-349 of SEQ ID NO:338, residues 2-349 of SEQ ID NO:341, residues 2-349 of SEQ ID NO:344, residues 2-349 of SEQ ID NO:347, residues 2-349 of SEQ 15 ID NO:350, residues 2-349 of SEQ ID NO:353, residues 2-349 of SEQ ID NO:356, residues 2-349 of SEQ ID NO:359, residues 2-349 of SEQ ID NO:362, residues 2-349 of SEQ ID NO:365, residues 2-349 of SEQ ID NO:368, residues 2-349 of SEQ ID NO:371, residues 2-349 of SEQ ID NO:374, residues 2-349 of SEQ ID NO:377, residues 2-349 of SEQ 20 ID NO:380, residues 2-349 of SEQ ID NO:383, residues 3-349 of SEQ ID NO:179, residues 2-349 of SEQ ID NO:182, residues 2-349 of SEQ ID NO:185, residues 2-349 of SEQ ID NO:188, residues 2-349 of SEQ ID NO:191, residues 2-25 349 of SEQ ID NO:194, residues 2-349 of SEQ ID NO:197, residues 2-349 of SEQ ID NO:200, residues 2-349 of SEQ ID NO:203, residues 2-349 of SEQ ID NO:206, residues 2-349 of SEQ ID NO:209, residues 2-349 of SEQ ID NO:212, residues 2-349 of SEQ ID NO:215, residues 2-349 of SEQ 30 ID NO:218, residues 2-349 of SEQ ID NO:221, residues 2-349 of SEQ ID NO:224, residues 2-349 of SEQ ID NO:227, residues 2-349 of SEQ ID NO:230, residues 2-349 of SEQ ID NO:233, residues 2-349 of SEQ ID NO:236, residues 2-349 of SEQ ID NO:239, residues 2-349 of SEQ ID NO:242, residues 2-349 of SEQ ID NO:245, residues 2-349 of SEQ 35

ID NO:248, residues 2-349 of SEQ ID NO:251, residues 2-349 of SEQ ID NO:254, residues 2-349 of SEO ID NO:257, residues 2-349 of SEQ ID NO:260, residues 2-349 of SEQ ID NO:263, residues 2-349 of SEQ ID NO:266, residues 2-349 of SEQ ID NO:269, residues 2-349 of SEQ ID NO:272, 5 residues 2-349 of SEQ ID NO:275, residues 2-349 of SEQ ID NO:278, residues 2-349 of SEQ ID NO:281, residues 2-349 of SEQ ID NO:284, residues 2-349 of SEQ ID NO:287, residues 2-349 of SEQ ID NO:290, residues 2-349 of SEQ 10 ID NO:293, residues 2-349 of SEQ ID NO:296, residues 2-349 of SEQ ID NO:299, residues 2-349 of SEQ ID NO:302, residues 2-349 of SEQ ID NO:305, residues 2-349 of SEQ ID NO:308, residues 2-349 of SEQ ID NO:311, residues 2-349 of SEQ ID NO:314, residues 2-349 of SEQ ID NO:317, 15 residues 2-349 of SEQ ID NO:320, residues 2-349 of SEQ ID NO:323, residues 2-349 of SEQ ID NO:326, residues 2-349 of SEQ ID NO:329, residues 2-349 of SEQ ID NO:332, residues 2-349 of SEQ ID NO:335, residues 2-349 of SEQ ID NO:338, residues 2-349 of SEQ ID NO:341, residues 2-20 349 of SEQ ID NO:344, residues 2-349 of SEQ ID NO:347, residues 2-349 of SEQ ID NO:350, residues 2-349 of SEQ ID NO:353, residues 2-349 of SEQ ID NO:356, residues 2-349 of SEQ ID NO:359, residues 2-349 of SEQ ID NO:362, residues 2-349 of SEQ ID NO:365, residues 2-349 of SEQ 25 ID NO:368, residues 2-349 of SEQ ID NO:371, residues 2-349 of SEQ ID NO:374, residues 2-349 of SEQ ID NO:377, residues 2-349 of SEQ ID NO:380, and residues 2-349 of SEQ ID NO:383.

30 6. The Myelopoietin conjugate of claim 1 wherein said Myelopoietin polypeptide is selected from the group consisting of: SEQ ID NO:224, residues 2-322 of SEQ ID NO:224, and residues 3-322 of SEQ ID NO:224.

7. The Myelopoietin conjugate of claim 1, 2, 3, 4, 5 or 6 wherein said polymer is a poly(ethylene oxide) molecule.

- 5 8. The Myelopoietin conjugate of claim 7 wherein said poly(ethylene oxide) molecule is a poly(ethylene glycol) molecule.
- 9. The Myelopoietin conjugate of claim
 10 8 wherein the poly(ethylene glycol) is attached at an amino acid residue having a free amino, carboxyl or sulfhydryl group(s).
- 10. The Myelopoietin conjugate of claim 9 wherein said poly(ethylene glycol) is conjugated through a activated poly(ethylene glycol).
- 11. The Myelopoietin conjugate of claim 10 wherein said activated poly(ethylene glycol) is selected from the group consisting of, para-nitrophenyl, succinimidyl, carbonyl imidazole, azlactones, cyclic imide thiones, isocyanates, isothiocyanates, aldehydes, primary amines, hydrazine, acyl hydrazides, carbazates, semicarbamates, thiocarbazates, thiols, maleimides, sulfones, and phenyl glyoxals.
 - 12. The Myelopoietin conjugate of claim 11 wherein said activated poly(ethylene glycol) is selected from the group consisting of, succinimidyl, carbonyl imidazole, aldehydes, acyl hydrazides, carbazates, semicarbamates, and maleimides.
- 13. The Myelopoietin conjugate of claim 9 wherein said poly(ethylene glycol) has a molecular weight of between about 0.5 kDa and about 100 kDa.

14. The Myelopoietin conjugate of claim 9 wherein said poly(ethylene glycol) has a molecular weight of between about 3.4 kDa and about 40 kDa.

5

- 15. The Myelopoietin conjugate of claim 9 wherein said poly(ethylene glycol) is a branched polymer.
- 16. The Myelopoietin conjugate of claim 15 wherein branched poly(ethylene glycol) polymer has a molecular weight of between about 10 kDa and about 40 kDa.
 - 17. The Myelopoietin conjugate of claim 9 wherein said poly(ethylene glycol) is a bifunctional polymer.

- 18. The Myelopoietin conjugate of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17 wherein said Myelopoietin conjugate is a prodrug.
- 20 19. A composition comprising the Myelopoietin of claim 1, 2, 3, 4, 5, 6, 7, 8, or 9 and at least one pharmaceutically acceptable carrier.
- 20. A composition comprising the Myelopoietin of claim 10 and at least one pharmaceutically acceptable carrier.
- 21. A composition comprising the Myelopoietin of claim 11, 12, 13, 14, 15, 16, 17, or 18 and at least one pharmaceutically acceptable carrier.
 - 22. A method of treating a patient having a hematopoietic disorder comprising administering to said patient a therapeutically effective amount of the

Myelopoietin conjugate of claim 1, 2, 3, 4, 5, 6, 7, 8, or 9.

- 23. A method of treating a patient having a 5 hematopoietic disorder comprising administering to said patient a therapeutically effective amount of the Myelopoietin conjugate of claim 10.
- 24. A method of treating a patient having a hematopoietic disorder comprising administering to said patient a therapeutically effective amount of the Myelopoietin conjugate of claim 11, 12, 13, 14, 15, 16, 17, or 18.
- 15 25. The method of claim 22 wherein said hematopoietic disorder is neutropenia, leukopenia, thrombocytopenia, or anemia.
- 26. The method of claim 23 wherein said 20 hematopoietic disorder is neutropenia, leukopenia, thrombocytopenia, or anemia.
- 27. The method of claim 24 wherein said hematopoietic disorder is neutropenia, leukopenia, thrombocytopenia, or anemia.

- 28. The method of claim 22 wherein said hematopoietic disorder is the result of chemotherapy, radiation therapy, or bone marrow suppressive drugs.
- 29. The method of claim 23 wherein said hematopoietic disorder is the result of chemotherapy, radiation therapy, or bone marrow suppressive drugs.
- 35 30. The method of claim 24 wherein said hematopoietic disorder is the result of chemotherapy, radiation therapy, or bone marrow suppressive drugs.

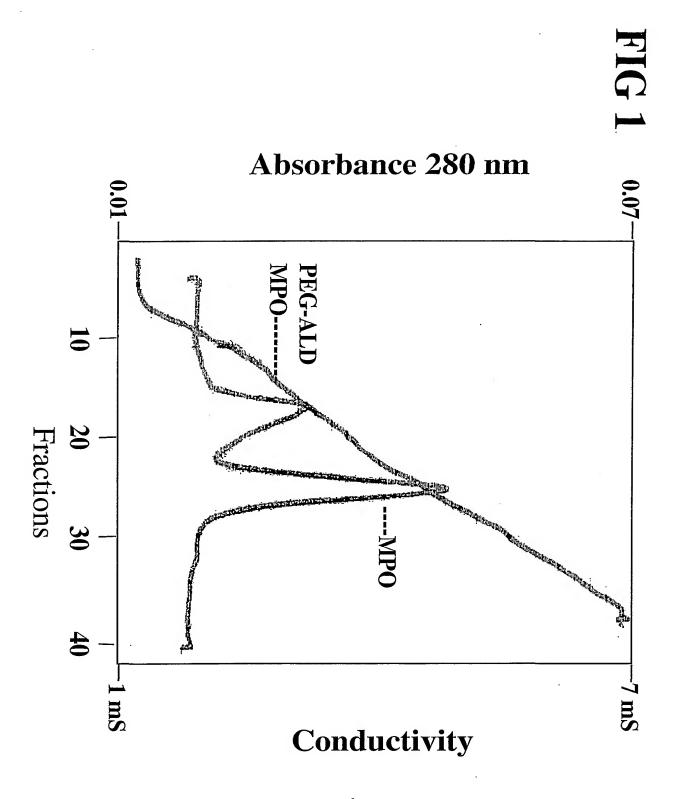
31. A method of treating a patient recovering and/or suffering from a bone marrow transplant, burn, wound, parasite, bacterial or viral infection comprising administering to said patient a therapeutically effective amount of the Myelopoietin conjugate of claim 1, 2, 3, 4, 5, 6, 7, 8, or 9.

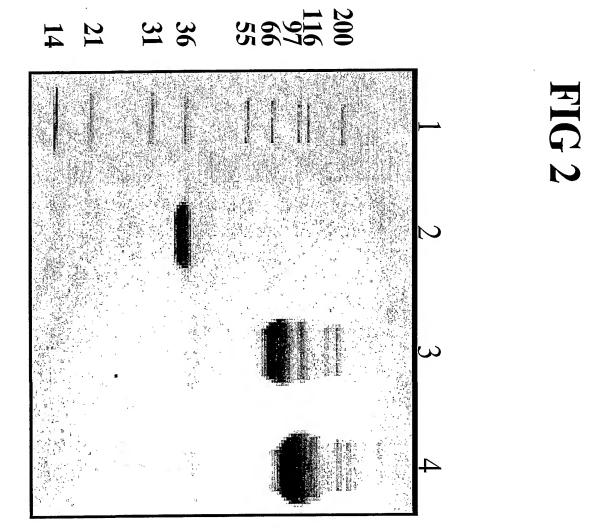
32. A method of treating a patient recovering
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10.

15

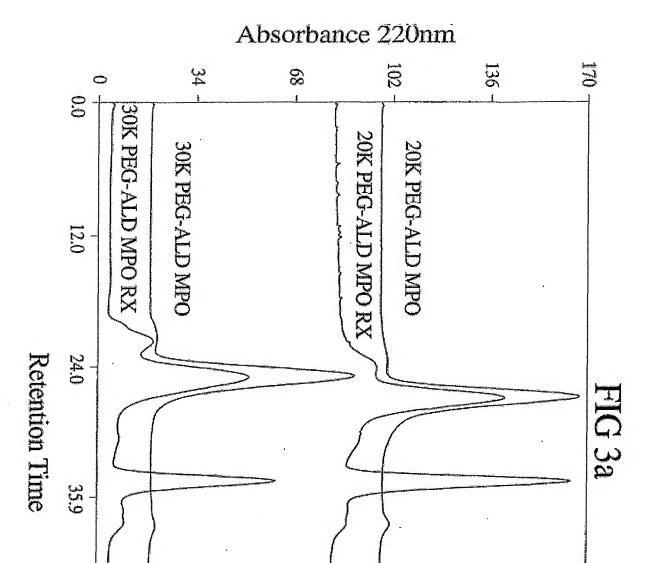
- 33. A method of treating a patient recovering and/or suffering from a bone marrow transplant, burn, wound, parasite, bacterial or viral infection comprising administering to said patient a therapeutically effective amount of the Myelopoietin conjugate of claim 11, 12, 13, 14, 15, 16, 17, or 18.
- 34. A method of mobilizing hematopoietic progenitors and stem cells into peripheral blood comprising administering to said patient a therapeutically effective amount of the Myelopoietin conjugate of claim 1, 2, 3, 4, 5, 6, 7, 8, or 9.
- 35. A method of mobilizing hematopoietic
 30 progenitors and stem cells into peripheral blood comprising administering to said patient a therapeutically effective amount of the Myelopoietin conjugate of claim 10.

36. A method of mobilizing hematopoietic progenitors and stem cells into peripheral blood comprising administering to said patient a therapeutically effective amount of the Myelopoietin conjugate of claim 11, 12, 13, 14, 15, 16, 17, or 18.



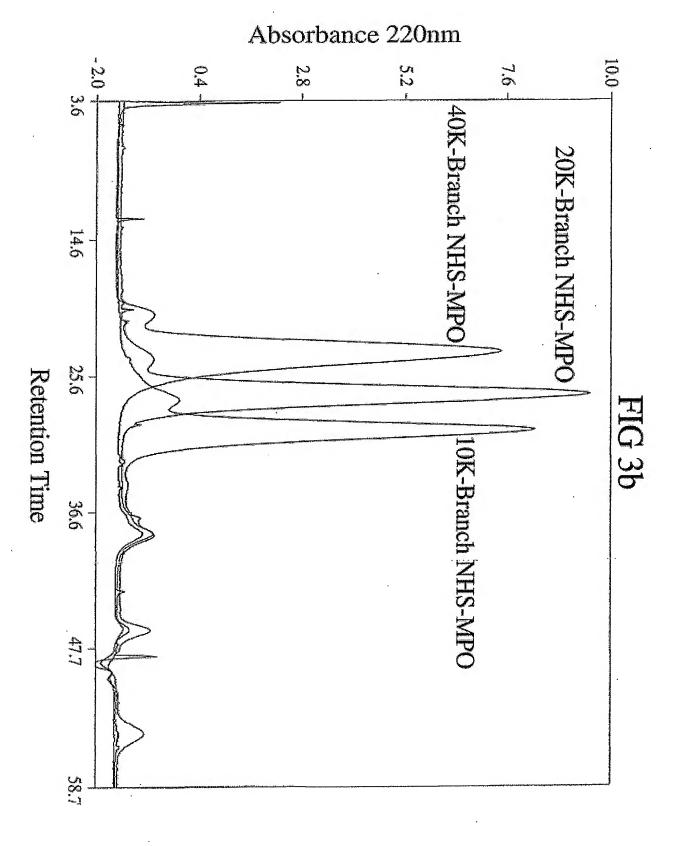


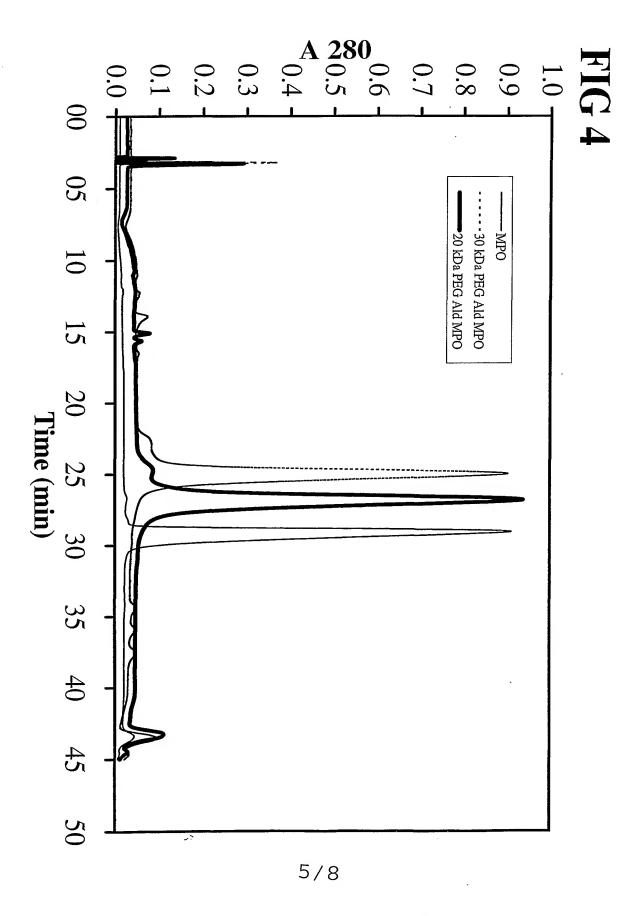
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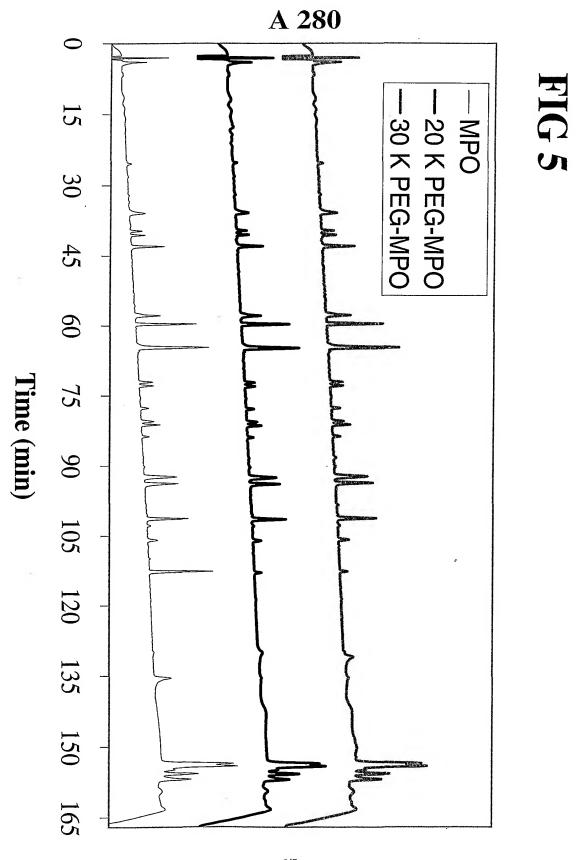


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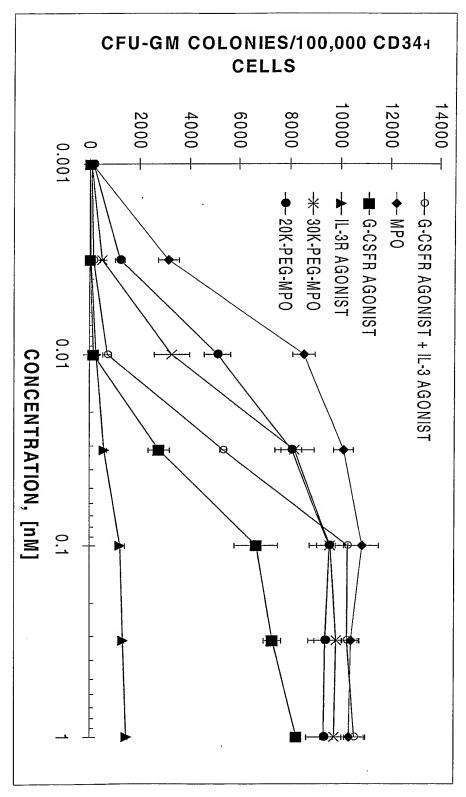
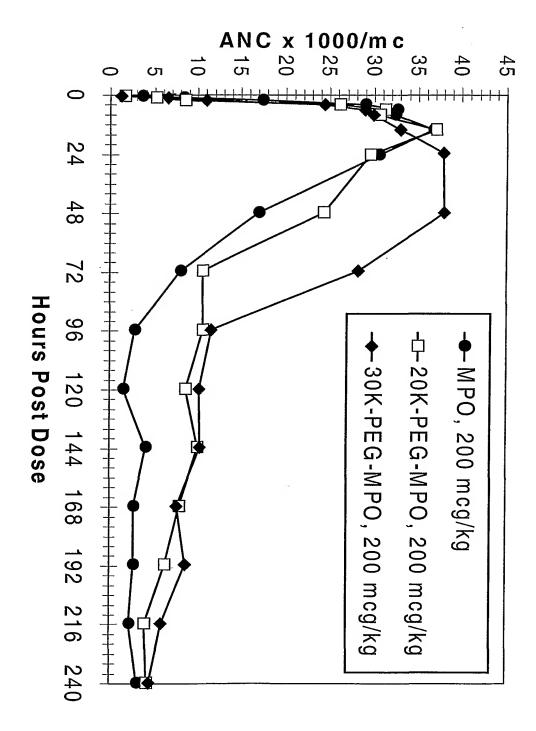


FIG 7



SEQUENCE LISTING

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             Rory F. Finn
             Kurt Sedo
             Yatin Gokarn
             Peter Nicastro
             Walter G. Smith
             Hong Qi
             Robert Hills
             Ned Siegel
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            Ser, Ala, Lys, Thr, Ile, Gly, or Pro"
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         /note= "Xaa at position 108 is Arg,
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            Lys, Asp, Leu, Thr, Ile, Gln, His, Ser, Ala, or Pro"
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            Thr, Pro, Glu, Tyr, Leu, Ser, or Gly"
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         /note= "Xaa at position 110 is Lys,
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Ala, Asn, Thr, Leu, Arg, Gln, His, Glu, Ser, Ala,
            or Trp"
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         /note= "Xaa at position 111 is Leu,
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           Ile, Arg, Asp, or Met"
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         /note= "Xaa at position 112 is Thr,
           Val, Gln, Tyr, Glu, His, Ser, or Phe"
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         /note= "Xaa at position 113 is Phe,
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            Ser, Cys, His, Gly, Trp, Tyr, Asp, Lys, Leu, Ile, Val,
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           Cys, His, Ser, Trp, Arg, or Leu"
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            Met"
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            Asn, His, Ala, Tyr, Phe, Gln, or Ile"
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           Ser, Asn, Ile, Trp, Lys, or Pro"
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         /note= "Xaa at position 118 is Leu,
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           Ser, Pro, Ala, Glu, Cys, Asp, or Tyr"
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         /note= "Xaa at position 119 is Glu,
           Ser, Lys, Pro, Leu, Thr, Tyr, or Arg"
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           Ala, Pro, Leu, His, Val, or Gln"
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         /note= "Xaa at position 121 is Ala,
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           Ser, Ile, Asn, Pro, Lys, Asp, or Gly"
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        /note= "Xaa at position 122 is
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Gln, Ser, Met, Trp, Arg, Phe, Pro, His, Ile, Tyr, or Cys" <220> <221> MUTAGEN <222> 123 <223> /note= "Xaa at position 123 is Ala, Met, Glu, His, Ser, Pro, Tyr, or Leu" <400> Ala Pro Met Thr Gln Thr Thr Ser Leu Lys Thr Ser Trp Val Asn Cys Xaa Xaa Xaa Xaa Xaa Xaa Asn Xaa Aaa Phe Xaa Xaa Xaa Xaa Xaa 100 105 115 120 Ser Leu Ala Ile Phe 130 <210> <211> 133 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> /note= "Met- may or may not precede <223> the amino acid in position 1" <220> MUTAGEN <221> <222> <223> /note= "Xaa at position 17 is Ser, Gly, Asp, Met, or Gln" <220> <221> MUTAGEN <222> <223> /note= "Xaa at position 18 is Asn, His, or Ile" <220> <221> MUTAGEN <222> /note= "Xaa at position 19 is Met <223> or Ile" <220> <221> MUTAGEN <222> /note="Xaa at position 21 is Asp or Glu" <220> <221> MUTAGEN <222> 23

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        /note= "Xaa at position 26 is His
           or Ala"
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         /note= "Xaa at position 29 is Gln,
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           Asn, or Val"
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           Gly, or Gln"
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        /note= "Xaa at position 31 is Pro,
           Asp, Gly, or Gln"
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            Thr, or Met"
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         /note= "Xaa at position 37 is Phe,
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           Ser, Pro, or Trp"
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        /note="Xaa at position 38 is Asn
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            or Glu"
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           Arg, Met, Pro, Ser, Thr, or His"
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            or Lys"
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           or Ser"
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          Pro, Thr, or Ile"
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        /note= "Xaa at position 63 is Arg
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           or Lys"
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         /note= "Xaa at position 65 is Val
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           or Thr"
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           or Arg"
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        /note= "Xaa at position 67 is Ser
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           Phe or His"
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        /note= "Xaa at position 68 is Leu,
           Ile, Phe, or His"
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         /note= "Xaa at position 69 is Gln,
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          Pro, or Arg"
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           Glu, Arg, or Asp"
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           or Leu"
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           or Leu"
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        /note= "Xaa at position 79 is
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         /note= "Xaa at position 80 is Asn,
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Met, Phe, Ser, Thr, Tyr, or Val"
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          or Val"
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            or Ser"
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         /note= "Xaa at position 88 is Ala
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           or Trp"
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        /note= "Xaa at position 91 is Ala
            or Pro"
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           Asp, Ser, Pro, Ala, Leu, or Arg"
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            Pro, Arg, Val, Leu, Gly, Asn, Phe, Ser, or Thr"
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         /note= "Xaa at position 96 is Pro
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           or Tyr"
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           or Val"
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           Leu, or Val"
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           or Leu"
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         /note= "Xaa at position 105 is
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           Asn, Pro, Ala, Ser, Trp, Gln, Tyr, Leu, Lys, Ile,
            Asp, or His"
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         /note="Xaa at position 108 is Arg,
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          Ala, or Ser"
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        /note= "Xaa at position 109 is Arg,
           Thr, Glu, Leu, or Ser"
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        /note= "Xaa at position 112 is Thr,
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           Val, or Gln"
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           or Trp"
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        /note= "Xaa at position 115 is Leu
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           or Ala"
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           Thr, Val, Trp, Ser, Ala, His, Met, Phe, Tyr, or Ile"
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Pro, Leu, His, Val, or Gln" <220> MUTAGEN <221> <222> 121 <223> /note= "Xaa at position 121 is Ala, Ser, Ile, Asn, Pro, Asp, or Gly" <220> <221> MUTAGEN <222> <223> /note= "Xaa at position 122 is Gln, Ser, Met, Trp, Arg, Phe, Pro, His, Ile, Tyr, <220> MUTAGEN <221> <222> /note= "Xaa at position 123 is Ala, Met, Glu, His, Ser, Pro, Tyr, or Leu" <400> Ala Pro Met Thr Gln Thr Thr Ser Leu Lys Thr Ser Trp Val Asn Cys Xaa Xaa Xaa Ile Xaa Glu Xaa Xaa Xaa Xaa Leu Lys Xaa Xaa Xaa Xaa Xaa Xaa Asp Xaa Xaa Asn Leu Asn Xaa Glu Xaa Xaa Xaa Ile Leu Met Xaa Xaa Asn Leu Xaa Xaa Xaa Asn Leu Glu Xaa Phe Xaa Xaa Xaa 55 Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ile Glu Xaa Xaa Leu Xaa Xaa 70 Leu Xaa Xaa Cys Xaa Pro Xaa Xaa Thr Ala Xaa Pro Xaa Arg Xaa Xaa Xaa Xaa Xaa Xaa Gly Asp Xaa Xaa Aaa Phe Xaa Xaa Lys Leu Xaa Phe Xaa Xaa Xaa Leu Glu Xaa Xaa Xaa Gln Gln Thr Thr Leu 115 120 Ser Leu Ala Ile Phe 130 <210> <211> 133 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> /note= "Met- may or may not precede <223> the amino acid in position 1" <220> <221> MUTAGEN <222> <223> /note= "Xaa at position 17 is Ser, Gly, Asp, or Gln" <220> <221> MUTAGEN <222> /note= "Xaa at position 18 is Asn, <223> His, or Ile" <220> <221> MUTAGEN

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            or Ala"
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        /note= "Xaa at position 46 is Asp,
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           Phe, Ser, Gln, Glu, His, Val, or Thr"
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        /note= "Xaa at position 50 is Glu,
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         /note= "Xaa at position 56 is Pro,
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           or Phe"
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           or Leu"
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Gly, Glu, or Arg"
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            Gln, Trp, Arg, Asp, Asn, Glu, His, Met, Phe, Ser, Thr, Tyr, or Val"
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           or Ser"
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            or Ser"
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          or Gln"
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Xaa Xaa Met Ile Asp Glu Xaa Ile Xaa Xaa Leu Lys Xaa Xaa Pro Xaa
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Pro Xaa Xaa Asp Phe Xaa Asn Leu Asn Xaa Glu Asp Xaa Xaa Ile Leu
Met Xaa Xaa Asn Leu Arg Xaa Xaa Asn Leu Glu Ala Phe Xaa Arg Xaa
Xaa Lys Xaa Xaa Xaa Asn Ala Ser Ala Ile Glu Xaa Xaa Leu Xaa Xaa
Leu Xaa Pro Cys Leu Pro Xaa Xaa Thr Ala Xaa Pro Xaa Arg Xaa Pro
Ile Xaa Xaa Xaa Kaa Gly Asp Trp Xaa Glu Phe Xaa Xaa Lys Leu Xaa
Phe Tyr Leu Xaa Xaa Leu Glu Xaa Xaa Xaa Gln Gln Thr Thr Leu
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Ser Leu Ala Ile Phe
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            or Gly"
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            Ile, or Met"
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Trp, or Arg"
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            Phe, Tyr, Ile, or Met"
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            Gly, or Ser"
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            Ala, or Pro"
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            Ser, Ala, Ile, Glu, His, or Trp"
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         /note= "Xaa at position 34 is Leu,
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            Met, Val, or Asn"
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           Arg, Ala, Gly, Pro, Asn, His, or Asp"
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            His, Phe, Met, or Gln"
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            Ala, Pro, Thr, Glu, Arg, Trp, Gly, or Leu"
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            or Leu"
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            Tyr, Phe, Ile, Met, or Val"
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Asp, Pro, Met, Lys, His, Thr, Val, Tyr, Glu, Asn,
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           Val, Gln, Tyr, Glu, His, Ser, or Phe"
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       /note= "Xaa at position 106 is Asn,
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         Ala, Pro, Leu, His, Val or Gln"
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       /note= "Xaa at position 107 is Ala,
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       /note= "Xaa at position 108 is
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         Gln, Ser, Met, Trp, Arg, Phe, Pro, His, Ile, Tyr,
         or Cys"
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       /note= "Xaa at position 109 is Ala,
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            Thr, or Met"
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Met, Glu, His, Ser, Pro, Tyr, or Leu"

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Xaa Xaa Xaa Xaa Xaa Asp Xaa Asn Leu Asn Xaa Glu Xaa Xaa Xaa 20 30

Ile Leu Met Xaa Xaa Asn Leu Xaa Xaa Xaa Asn Leu Glu Xaa Phe Xaa 35 40 45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ile Glu Xaa Xaa Leu

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Xaa Xaa Leu Xaa Xaa Cys Xaa Pro Xaa Xaa Thr Ala Xaa Pro Xaa Arg
                    70
Xaa Xaa Xaa Xaa Xaa Xaa Cly Asp Xaa Xaa Aaa Phe Xaa Xaa Lys
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Leu Xaa Phe Xaa Xaa Xaa Xaa Leu Glu Xaa Xaa Xaa Gln Gln
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           or Phe"
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Pro Xaa Pro Xaa Xaa Asp Phe Xaa Asn Leu Asn Xaa Glu Asp Xaa Xaa
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                                25
Ile Leu Met Xaa Xaa Asn Leu Arg Xaa Xaa Asn Leu Glu Ala Phe Xaa
Arg Xaa Xaa Lys Xaa Xaa Xaa Asn Ala Ser Ala Ile Glu Xaa Xaa Leu
Xaa Xaa Leu Xaa Pro Cys Leu Pro Xaa Xaa Thr Ala Xaa Pro Xaa Arg
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Leu Xaa Phe Tyr Leu Xaa Xaa Leu Glu Xaa Xaa Xaa Gln Gln
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or Leu"

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        /note= "Xaa at position 85 is Leu
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         /note= "Xaa at position 87 is Leu,
<223>
           Ser, or Tyr"
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        /note= "Xaa at position 88 is Ala
<223>
          or Trp"
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         /note= "Xaa at position 91 is Ala
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           or Pro"
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         93
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        /note= "Xaa at position 93 is Pro
           or Ser"
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        /note= "Xaa at position 95 is His
<223>
           or Thr"
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         98
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        /note= "Xaa at position 98 is His,
           Ile, or Thr"
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        /note= "Xaa at position 100 is Lys
<223>
           or Arg"
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         /note= "Xaa at position 101 is Asp,
           Ala, or Met"
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        /note= "Xaa at position 105 is Asn
          or Glu"
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        109
        /note= "Xaa at position 109 is Arg,
<223>
           Glu, or Leu"
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         112
        /note= "Xaa at position 112 is Thr
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           or Gln"
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        /note= "Xaa at position 116 is Lys,
<223>
           Val, Trp, or Ser"
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        /note= "Xaa at position 117 is Thr
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           or Ser"
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        /note= "Xaa at position 120 is Asn,
<223>
            Gln, or His"
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        /note= "Xaa at position 123 is Ala
           or Glu"
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Ala Pro Met Thr Gln Thr Thr Ser Leu Lys Thr Ser Trp Val Asn Cys
Ser Xaa Xaa Xaa Asp Glu Xaa Ile Xaa His Leu Lys Xaa Pro Pro Xaa
Pro Xaa Leu Asp Xaa Xaa Asn Leu Asn Xaa Glu Asp Xaa Xaa Ile Leu
Xaa Xaa Xaa Asn Leu Arg Xaa Xaa Asn Leu Xaa Xaa Phe Xaa Xaa Ala
Xaa Lys Xaa Leu Xaa Asn Ala Ser Xaa Ile Glu Xaa Ile Leu Xaa Asn
Leu Xaa Pro Cys Xaa Pro Xaa Xaa Thr Ala Xaa Pro Xaa Arg Xaa Pro
Ile Xaa Ile Xaa Xaa Gly Asp Trp Xaa Glu Phe Arg Xaa Lys Leu Xaa
                               105
Phe Tyr Leu Xaa Xaa Leu Glu Xaa Ala Gln Xaa Gln Gln Thr Thr Leu
                            120
Ser Leu Ala Ile Phe
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         /note= "Xaa at position 5 is Met,
<223>
           Ala, or Ile"
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         /note= "Xaa at position 6 is Ile,
<223>
          Pro, or Leu"
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        /note= "Xaa at position 9 is Ile,
           Ala, or Leu"
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         11
         /note= "Xaa at position 11 is Thr
<223>
           or His"
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        /note= "Xaa at position 15 is Gln,
           Arg, Val, or Ile"
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        /note= "Xaa at position 18 is Leu,
<223>
          Ala, Asn, or Arg"
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        /note= "Xaa at position 20 is Leu
           or Ser"
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         /note= "Xaa at position 23 is Phe,
          Pro, or Ser"
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         /note= "Xaa at position 24 is Asn
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         28
         /note= "Xaa at position 28 is Gly,
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          Ala, Ser, Asp, or Asn"
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        /note= "Xaa at position 31 is Gln,
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        /note= "Xaa at position 32 is Asp
           or Ser"
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        /note= "Xaa at position 35 is Met,
<223>
           Ile, or Asp"
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        37
         /note= "Xaa at position 37 is Asn,
<223>
           Arg, or Ser"
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        /note= "Xaa at position 41 is Arg,
           Leu, or Thr"
<220>
<221>
        MUTAGEN
<222>
        42
        /note= "Xaa at position 42 is Pro
<223>
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or Ser" <220> <221> MUTAGEN <222> 45 /note= "Xaa at position 45 is Glu <223> or Leu" <220> <221> MUTAGEN <222> 46 <223> /note= "Xaa at position 46 is Ala or Ser" <220> <221> MUTAGEN <222> <223> /note= "Xaa at position 48 is Asn, Val, or Pro" <220> <221> MUTAGEN <222> 49 /note= "Xaa at position 49 is Arg <223> or His" <220> <221> MUTAGEN <222> /note= "Xaa at position 51 is Val <223> or Ser" <220> <221> MUTAGEN <222> 53 /note= "Xaa at position 53 is Ser, <223> Asn, His, or Gln" <220> <221> MUTAGEN <222> <223> /note= "Xaa at position 55 is Gln or Glu" <220> <221> MUTAGEN <222> 59 /note= "Xaa at position 59 is Ala <223> or Gly" <220> MUTAGEN <221> <222> 62 <223> /note= "Xaa at position 62 is Ser, Ala, or Pro" <220> MUTAGEN <221> <222> <223> /note= "Xaa at position 65 is Lys, Arg, or Ser" <220> <221> MUTAGEN <222> 67 /note= "Xaa at position 67 is Leu, <223> Glu, or Val" <220> MUTAGEN <221> <222> /note= "Xaa at position 68 is Leu, <223> Glu, Val, or Trp" <220>

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MUTAGEN

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        /note= "Xaa at position 73 is Leu,
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        /note= "Xaa at position 74 is Ala
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           or Trp"
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        /note= "Xaa at position 77 is Ala
          or Pro"
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        /note= "Xaa at position 79 is Pro
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           or Ser"
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        /note= "Xaa at position 81 is His
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        /note= "Xaa at position 84 is His,
           Ile, or Thr
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        /note= "Xaa at position 86 is Lys
          or Arg"
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        /note= "Xaa at position 87 is Asp,
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           Ala, or Met"
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        /note= "Xaa at position 91 is Asn
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           or Glu"
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        /note= "Xaa at position 95 is Arg,
           Glu, or Leu"
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        /note= "Xaa at position 98 is Thr
<223>
           or Gln"
<220>
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<221>
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        102
<223>
        /note= "Xaa at position 102 is Lys,
           Val, Trp, or Ser"
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        /note= "Xaa at position 103 is Thr
<223>
           or Ser"
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<221>
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         106
        /note= "Xaa at position 106 is Asn,
<223>
          Gln, or His"
<220>
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         /note= "Xaa at position 109 is Ala
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            or Glu"
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Pro Xaa Pro Xaa Leu Asp Xaa Xaa Asn Leu Asn Xaa Glu Asp Xaa Xaa
Ile Leu Xaa Xaa Xaa Asn Leu Arg Xaa Xaa Asn Leu Xaa Xaa Phe Xaa
Xaa Ala Xaa Lys Xaa Leu Xaa Asn Ala Ser Xaa Ile Glu Xaa Ile Leu
Xaa Asn Xaa Xaa Pro Cys Xaa Pro Xaa Xaa Thr Ala Xaa Pro Xaa Arg
Xaa Pro Ile Xaa Ile Xaa Xaa Gly Asp Trp Xaa Glu Phe Arg Xaa Lys
Leu Xaa Phe Tyr Leu Xaa Xaa Leu Glu Xaa Ala Gln Xaa Gln Gln
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Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Ala Glu Asp Val Asp
Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn
Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu
Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg 65 70 75 80
His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys
Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln
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Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp
Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn
                            40
Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu
Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg 65 70 75 80
His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys
Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln
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        1-111
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Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Val Pro
Pro Ala Pro Leu Leu Asp Ser Asn Asn Leu Asn Ser Glu Asp Met Asp
Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn
Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu
Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg
His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys
Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln
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        1-111
<223>
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Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp 25 Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Leu Ala Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln <210> 13 <211> 111 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-111 <223> <400> Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln <210> 14 <211> 111 <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-111 <223> <400> Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Ala Ile Glu Ser Ile Leu

50 55 60 Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln <210> 15 <211> 111 <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-111 <223> <400> Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg 65 70 75 80 His Pro Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln <210> 16 <211> 111 <212> PRT Artificial Sequence <220> <221> MUTAGEN <222> 1-111 <223> <400> Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn 40 Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Arg Lys

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<212>
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<213>
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<221>
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<222>
        1-111
<223>
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Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp
Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn
Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu
Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg 65 70 75 80
His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Glu Lys 85 90 95
Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln
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        1-111
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Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp
Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn
Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu
Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg
His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Glu Lys 85 90 95
Leu Thr Phe Tyr Leu Val Ser Leu Glu His Ala Gln Glu Gln Gln
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        1-111
<223>
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<400> Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln <210> 20 <211> 111 <212> <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-111 <223> <400> Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln 105 <210> 21 <211> 111 <212> PRT Artificial Sequence <220> MUTAGEN <221> <222> 1-111 <223> <400> 21 Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp

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Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn

Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly Ile Glu Ala Ile Leu 55 Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Ser Leu Glu His Ala Gln Glu Gln <210> 22 <211> 111 <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-111 <223> <400> Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro 10 Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Ala Glu Asp Val Asp Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg 65 70 75 80 His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln 105 <210> 23 <211> 111 <212> PRT <213> Artificial Sequence <220> MUTAGEN <221> <222> 1-111 <223> <400> Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg

His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys

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Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln
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Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Val Pro
                                    10
Pro Ala Pro Leu Leu Asp Ser Asn Asn Leu Asn Ser Glu Asp Met Asp
                               25
Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Leu Ala Phe Val
Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Ala Ile Glu Ser Ile Leu
Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg 65 70 75 80
His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys
Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln
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Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys
Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp
Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala
Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly Ile Glu Ala
Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
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<212>
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<222>
        1-113
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Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp
Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala
Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly Ile Glu Ala
Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
                               105
Gln
<210>
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<212>
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<213>
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<222>
        1-113
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Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys
Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp
Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala
Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly Ile Glu Ala
Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
Glu Lys Leu Thr Phe Tyr Leu Val Ser Leu Glu His Ala Gln Glu Gln
                                105
Gln
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       1-113
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Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Ala Glu Asp
Val Asp Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Ala Ile Glu Ser
Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro
Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg
                                   90
Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln
Gln
<210>
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Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala
Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Ala Ile Glu Ser
Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro
Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg
Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln
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Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Ala Ile Glu Ser
Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro
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Val Asp Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala
Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
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Val Asp Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser

35 40 45 Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln 105 Gln <210> 35 <211> 113 <212> PRT <213> Artificial Sequence <220> MUTAGEN <221> <222> 1-113 <223> <400> Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Val Pro Pro Ala Pro Leu Leu Asp Ser Asn Asn Leu Asn Ser Glu Asp 25 Met Asp Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Leu Ala 40 Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg 90 Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln <210> 36 <211> 113 <212> PRT Artificial Sequence <213> <220> MUTAGEN <221> <222> 1-113 <223> <400> Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala

55

Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Ser Leu Glu His Ala Gln Glu Gln 105 Gln <210> 37 <211> 113 <212> PRT <213> Artificial Sequence <220> MUTAGEN <221> <222> 1-113 <223> <400> Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Val Pro Pro Ala Pro Leu Leu Asp Ser Asn Asn Leu Asn Ser Glu Asp 25 Met Asp Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Leu Ala Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Ser Leu Glu His Ala Gln Glu Gln Gln <210> 38 <211> 113 <212> PRT Artificial Sequence <213> <220> MUTAGEN <221> <222> 1-113 <223> <400> Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala 40 Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro

Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg 90 Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln 105 Gln <210> 39 <211> 113 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-113 <223> <400> Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Ala Glu Asp 25 Val Asp Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Ser Leu Glu His Ala Gln Glu Gln 105 Gln <210> 40 <211> 113 <212> PRT Artificial Sequence <213> <220> MUTAGEN <221> <222> 1-113 <223> <400> Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Ala Glu Asp Val Asp Ile Leu Met Asp Arg Asn Leu Arg Leu Ser Asn Leu Glu Ser 40 Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln

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Val Asp Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala
Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
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Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
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Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp
Val Ser Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala
Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
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Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp
Met Ser Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala
Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro 65 70 75 80
Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
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Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala
Pro Leu Leu Asp Pro Asn Asn Leu Asn Ala Glu Asp Val Asp Ile Leu
Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala
Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn
Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr
Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln
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Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe Val Arg Ala
Val Lys His Leu Glu Asn. Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn
Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr
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Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln
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Ile Pro Pro Asn Pro Ser Leu Asp Ser Ala Asn Leu Asn Ser Glu Asp
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Val Ser Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala
Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala
Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
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Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro
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Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg
              55
Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys
Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His
Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu
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Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Thr Thr
                          120
Leu Ser Leu Ala Ile Phe
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Ser Glu Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser
Gly Gly Gly Ser
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Ser Lys Glu Ser His Lys Ser Pro
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Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro
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Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala
Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser
Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro
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Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala
                           40
Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser
Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro
Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg
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Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala
Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser
Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro
Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg
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Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala
Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser
Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro
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Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln
                                105
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Gln Pro Pro L

2

Gln Asp Ile L

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Phe Asn Arg A

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Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Leu Glu Asp 20 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala $35 \hspace{1cm} 40 \hspace{1cm} 45$

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 100 105 110

Gln

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Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 100 105 110

Gln

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Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Tyr Glu Asp 25 Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 40 Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln <210> 60 <211> 113 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-113 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Ala Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln<210> <211> 113 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-113 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 25 Val Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser

55 Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln <210> <211> 113 <212> PRT Artificial Sequence <220> MUTAGEN <221> <222> 1-113 <400> 62 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Met Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 40 Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 90 Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln <210> 63 113 <211> <212> PRT Artificial Sequence <220> <221> MUTAGEN <222> 1-113 <223> <400> 63 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Asn Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 40 Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro

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Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 55 60

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Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser

50 55 60 Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg Thr Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln <210> 88 <211> 113 <212> Artificial Sequence <213> <220> MUTAGEN <221> <222> 1-113 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 25 Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg Asn Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95 Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln <210> <211> 113 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-113 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 25 Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro

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Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Pro Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln <210> 101 <211> 113 <212> Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-113 <223> <400> 101 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 40 Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys His Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln<210> 102 <211> 113 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-113 <223> <400> 102 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp . 25 Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asn Gly Asp Trp Asn Glu Phe Arg

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Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser
Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro
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Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser
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Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser
Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80
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Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro
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Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 90 Arg Lys Leu Thr Phe Tyr Leu Tyr Thr Leu Glu Asn Ala Gln Ala Gln Gln <210> 114 <211> 113 <212> PRT<213> Artificial Sequence <220> MUTAGEN <221> <222> 1-113 <223> <400> 114 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ile Gln Ala Gln Gln <210> 115 <211> 113 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-113 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 10 Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg

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Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro
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Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro
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Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 200 Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 215 Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln 235 Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser 280 His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 295 Ala Gln Pro 305 122 <210> <211> 307 <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-307 <223> <400> 122 Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys 10 Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp \cdot 25 \cdot 30 Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 120 Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp 150 155 Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His 170 Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 185 Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala

215 210 220 Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 265 Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 305 <210> 123 <211> 307 <212> PRT Artificial Sequence <220> MUTAGEN <221> <222> 1-307 <223> <400> 123 Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln 105 Gln Tyr Val Ile Glu Gly Lys Ile Ser Pro Gly Gly Gly Ser Gly Gly 120 Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 200 Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 215

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Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln

Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu 250 Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 305 <210> 124 <211> 307 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-307 <223> <400> 124 Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln Tyr Val Glu Gly Gly Gly Ser Pro Gly Gly Gly Ser Gly Gly Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Gly His Ser Leu Gly Ile Pro Trp Ala 185 Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 215 Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln 235 Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu

Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 265 Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 305 <210> 125 <211> 244 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-244 <223> <400> Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 120 Gly Ser Asn Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His 135 His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala 235 Gln Glu Gln Gln <210> 126 <211> <212> PRT

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Artificial Sequence

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Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala 55 Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln Tyr Val Glu Gly Gly Gly Ser Pro Gly Gly Gly Ser Gly Gly Gly Ser Asn Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His 135 His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln <210> 128 <211> 322 <212> PRT <213> Artificial Sequence <220> MUTAGEN <221> <222> 1-322 <223> <400> 128 Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala 40 Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 120

Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 135 Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser 150 Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 215 Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu 265 Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 129 <211> 322 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-322 <223> <400> Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala 55 Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln Tyr Val Ile Glu Gly Lys Ile Ser Pro Gly Glu Pro Ser Gly Pro 120 Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser

140 135 130 Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly 165 170 175 Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 185 Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 200 Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu 265 Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His 295 Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 130 <211> <212> PRT Artificial Sequence <213> <220> MUTAGEN <221> <222> 1-322 <223> Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln Tyr Val Glu Gly Gly Gly Ser Pro Gly Glu Pro Ser Gly Pro

Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser

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Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 185 Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 230 235 Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His 295 Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala 315 Gln Pro <210> 131 <211> 259 <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-259 <223> <400> 131 Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys 10 Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala 55 Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser

Pro Asn Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His 150 Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala 215 Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln <210> 132 <211> 259 <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-259 <223> <400> 132 Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro 65 70 75 80 Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln Tyr Val Ile Glu Gly Lys Ile Ser Pro Gly Glu Pro Ser Gly Pro 120 Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala

210 215 220

Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu 225 230 235 240

Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln 245 250 255

Glu Gln Gln

<210> 133

<211> 259 <212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN

<222> 1-259

<223>

<400> 133

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys 1 $$ 5 $$ 10 $$ 15

Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp 20 25 30

Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala 35 40 45

Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala 50 60

Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro 65 70 75 80

Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg 85 90 95

Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln 100 105 110

Gln Tyr Val Glu Gly Gly Gly Ser Pro Gly Glu Pro Ser Gly Pro 115 120 125

Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 130 135 140

Pro Asn Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His 145 150 155 160

Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser 165 170 175

Glu Asp Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu 180 185 190

Leu Ala Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile 195 200 205

Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala 210 215 220

Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu 225 230 235 240

Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln 245 250 255

Glu Gln Gln

<210> 134 <211> 307

PRT <212> <213> Artificial Sequence <220> MUTAGEN <221> <222> 1-307 <400> 134 Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 115 120 125 Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp 155 Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 215 Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 135 <211> 307 <212> PRT Artificial Sequence <213> <220>

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Arg Pro	Pro A 2		Leu	Leu	Asp	Pro 25	Asn	Asn	Leu	Asn	Asp 30	Glu	Asp
Val Ser	Ile L	eu Met	Asp	Arg	Asn 40	Leu	Arg	Leu	Pro	Asn 45	Leu	Glu	Ser
Phe Val 50	Arg A	la Val	Lys	Asn 55	Leu	Glu	Asn	Ala	Ser 60	Gly	Ile	Glu	Ala
Ile Leu 65	Arg A	sn Leu	Gln 70	Pro	Cys	Leu	Pro	<i>S</i> er 75	Ala	Thr	Ala	Ala	Pro 80
Ser Arg	His P	ro Ile 85	Ile	Ile	Lys	Ala	Gly 90	Asp	Trp	Gln	Glu	Phe 95	Arg
Glu Lys		hr Phe 00	Tyr	Leu	Val	Thr 105	Leu	Glu	Gln	Ala	Gln 110	Glu	Gln
Gln Tyr	Val I 115	le Glu	Gly	Arg	Ile 120	Ser	Pro	Gly	Gly	Gly 125	Ser	Gly	Gly
Gly Ser 130	Asn M	et Ala	Thr	Pro 135	Leu	Gly	Pro	Ala	Ser 140	Ser	Leu	Pro	Gln
Ser Phe 145	Leu L	eu Lys	Ser 150	Leu	Glu	Gln	Val	Arg 155	Lys	Ile	Gln	Gly	Asp 160
Gly Ala	Ala L	eu Gln 165	Glu	Lys	Leu	Cys	Ala 170	Thr	Tyr	Lys	Leu	Cys 175	His
Pro Glu		eu Val 80	Leu	Leu	Gly	His 185	Ser	Leu	Gly	Ile	Pro 190	Trp	Ala
Pro Leu	Ser Ser Ser 195	er Cys	Pro	Ser	Gln 200	Ala	Leu	Gln	Leu	Ala 205	Gly	Cys	Leu
Ser Gln 210		is Ser	Gly	Leu 215	Phe	Leu	Tyr	Gln	Gly 220	Leu	Leu	Gln	Ala
Leu Glu 225	Gly I	le Ser	Pro 230	Glu	Leu	Gly	Pro	Thr 235	Leu	Asp	Thr	Leu	Gln 240
Leu Asp	Val A	la Asp 245	Phe	Ala	Thr	Thr	Ile 250	Trp	Gln	Gln	Met	Glu 255	Glu
Leu Gly		la Pro 60	Ala	Leu	Gln	Pro 265	Thr	Gln	Gly	Ala	Met 270	Pro	Ala
Phe Ala	Ser A	la Phe	Gln	Arg	Arg 280	Ala	Gly	Gly	Val	Leu 285	Val	Ala	Ser
His Leu 290	Gln S	er Phe	Leu	Glu 295	Val	Ser	Tyr	Arg	Val 300	Leu	Arg	His	Leu
Ala Gln 305	Pro												
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<220> <221> <222> <223>	MUTA(1-24												

<400> 136

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys 1 5 10 15

Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp 20 25 30

Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser 35 40 45

Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala 50 60

Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro 65 70 75 80

Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg 85 90 95

Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln 100 105 110

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 115 120 125

Gly Ser Asn Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His 130 135 140

His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn 145 150 150 160

Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn 165 170 175

Leu Glu Ser Phe Val Arg Ala Val Lys As
n Leu Glu As
n Ala Ser Gly 180 \cdot 185 $$ 190

Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr 195 200 205

Ala Ala Pro Ser Arg His Pro Ile Ile Lys Ala Gly Asp Trp Gln 210 215 220

Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala 225 230 235 240

Gln Glu Gln Gln

<210> 137

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<220>

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<223>

<400> 137

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys

1 5 - 10 15

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Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser 35 40 45

Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala 50 55 60

Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro 65 70 75 80

Ser Arg His Pro Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu 185 Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln 138 <210> <211> 322 <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-322 <223> <400> 138 Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser

Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser 150 155 Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly 170 Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 215 Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe 280 Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His 295 Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 139 <211> 349 <212> PRT Artificial Sequence <220> MUTAGEN <221> <222> 1-349 <223> <400> Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala Gly Gly Gly Ser Gly Gly Ser Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser

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150
145
                                     155
Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr
Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser
                    185
Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu
Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu
                       215
Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro
Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly
Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro
                              265
Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe
                           280
Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala
Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln
Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu
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Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
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Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp
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Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala
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Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly Gly Ser Asn Met Ala Pro Ala Arg Ser Pro Ser Pro Ser Thr Gln Pro 135 Trp Glu His Val Asn Ala Ile Gln Glu Ala Arg Arg Leu Leu Asn Leu Ser Arg Asp Thr Ala Ala Glu Met Asn Glu Thr Val Glu Val Ile Ser Glu Met Phe Asp Leu Gln Glu Pro Thr Cys Leu Gln Thr Arg Leu Glu Leu Tyr Lys Gln Gly Leu Arg Gly Ser Leu Thr Lys Leu Lys Gly Pro Leu Thr Met Met Ala Ser His Tyr Lys Gln His Cys Pro Pro Thr Pro Glu Thr Ser Cys Ala Thr Gln Ile Ile Thr Phe Glu Ser Phe Lys Glu Asn Leu Lys Asp Phe Leu Leu Val Ile Pro Phe Asp Cys Trp Glu Pro Val Gln Glu <210> 142 <211> 301 <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-301 <223> <400> Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp 25 Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Glu Gly Gly Gly 135 Ser Glu Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Pro Ala Arg Ser Pro Ser Pro Ser Thr Gln Pro Trp Glu His Val Asn Ala Ile Gln Glu Ala Arg Arg Leu Leu Asn Leu Ser Arg Asp Thr Ala Ala 200 Glu Met Asn Glu Thr Val Glu Val Ile Ser Glu Met Phe Asp Leu Gln 215 Glu Pro Thr Cys Leu Gln Thr Arg Leu Glu Leu Tyr Lys Gln Gly Leu Arg Gly Ser Leu Thr Lys Leu Lys Gly Pro Leu Thr Met Met Ala Ser His Tyr Lys Gln His Cys Pro Pro Thr Pro Glu Thr Ser Cys Ala Thr Gln Ile Ile Thr Phe Glu Ser Phe Lys Glu Asn Leu Lys Asp Phe Leu 280 Leu Val Ile Pro Phe Asp Cys Trp Glu Pro Val Gln Glu <210> 335 <211> <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-335 <223> <400> Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln Tyr Val Pro Val Asn Ala Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly 130 \$135\$Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asn Met

145 150 155 Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu 170 Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser 215 Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 325 330 <210> 144 <211> 274 <212> PRT <213> Artificial Sequence <220> MUTAGEN <221> <222> 1-274 <223> <400> 144 Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala 40 Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg 90 Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 135 Pro Asn Met Ala Pro Ala Arg Ser Pro Ser Pro Ser Thr Gln Pro Trp 150 155

Glu His Val Asn Ala Ile Gln Glu Ala Arg Arg Leu Leu Asn Leu Ser 170 Arg Asp Thr Ala Ala Glu Met Asn Glu Thr Val Glu Val Ile Ser Glu Met Phe Asp Leu Gln Glu Pro Thr Cys Leu Gln Thr Arg Leu Glu Leu 200 Tyr Lys Gln Gly Leu Arg Gly Ser Leu Thr Lys Leu Lys Gly Pro Leu Thr Met Met Ala Ser His Tyr Lys Gln His Cys Pro Pro Thr Pro Glu Thr Ser Cys Ala Thr Gln Ile Ile Thr Phe Glu Ser Phe Lys Glu Asn Leu Lys Asp Phe Leu Leu Val Ile Pro Phe Asp Cys Trp Glu Pro Val 265 Gln Glu <210> 145 <211> 317 <212> PRT Artificial Sequence <213> <220> MUTAGEN <221> <222> 1-317 <223> <400> 145 Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys 10 Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 120 Gly Ser Asn Met Ala Pro Val Pro Pro Gly Glu Asp Ser Lys Asp Val 135 Ala Ala Pro His Arg Gln Pro Leu Thr Ser Ser Glu Arg Ile Asp Lys Gln Ile Arg Tyr Ile Leu Asp Gly Ile Ser Ala Leu Arg Lys Glu Thr Cys Asn Lys Ser Asn Met Cys Glu Ser Ser Lys Glu Ala Leu Ala Glu Asn Asn Leu Asn Leu Pro Lys Met Ala Glu Lys Asp Gly Cys Phe Gln

Ser Gly Phe Asn Glu Glu Thr Cys Leu Val Lys Ile Ile Thr Gly Leu 215 Leu Glu Phe Glu Val Tyr Leu Glu Tyr Leu Gln Asn Arg Phe Glu Ser 235 Ser Glu Glu Gln Ala Arg Ala Val Gln Met Ser Thr Lys Val Leu Ile 250 Gln Phe Leu Gln Lys Lys Ala Lys Asn Leu Asp Ala Ile Thr Thr Pro Asp Pro Thr Thr Asn Ala Ser Leu Leu Thr Lys Leu Gln Ala Gln Asn Gln Trp Leu Gln Asp Met Thr Thr His Leu Ile Leu Arg Ser Phe Lys 295 Glu Phe Leu Gln Ser Ser Leu Arg Ala Leu Arg Gln Met <210> 146 <211> 307 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-307 <223> Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 185 Ser Asn Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His 200 Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu

225 230 235 240 Leu Ala Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile 245 250 Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu 280 Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln 295 Glu Gln Gln 305 <210> 147 <211> <212> PRT Artificial Sequence <213> <220> MUTAGEN <221> <222> 1-307 <223> <400> 147 Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gl
n Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu 40 Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser 135 Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly Gly Ser Asn Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu 235 Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile 245

Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala 265 Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln 295 Glu Gln Gln <210> 148 <211> 337 <212> PRT<213> Artificial Sequence <220> MUTAGEN <221> <222> 1-337 <223> <400> 148 Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Tyr Val Pro Gln Pro Pro Val Asn Ala Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Glu 195 200 205 Gly Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly 210 \$215\$Asp Phe Asp Tyr Glu Asn Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg

Leu Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala 280 Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro 295 Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln <210> 149 <211> 322 <212> PRT Artificial Sequence <220> <221> MUTAGEN <222> 1-322 <400> 149 Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val 105 Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met 120 Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu'Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro 200 Asn Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu 215 Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu

260 265 270

Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala 275 280 285

Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe 290 295 300

Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu 305 310 315 320

Gln Gln

<210> 150

<211> 322 <212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN

<222> 1-322

<223>

<400> 150

Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu 1 5 10 15

Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala 20 25 30

Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu 35 40 45

Leu Val Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser 50 60

Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu 65 70 75 80

His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly 85 90 95

Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val 100 105 110

Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met 115 120 125

Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser 130 135 140

Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln 145 150 155 160

Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro $165 \hspace{1.5cm} 170 \hspace{1.5cm} 175$

Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro Ile 180 185 190

Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro 195 200 205

Asn Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu 210 215 220

Lys Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu 225 230 235 240

Asp Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu 245 250 255

Ala Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu 260 265 270

Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln <210> 151 <211> 349 <212> PRT Artificial Sequence <213> <220> MUTAGEN <221> <222> 1-349 <223> <400> 151 Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala Gly 185 Gly Gly Ser Gly Gly Gly Ser Gly Gly Ser Glu Gly Gly Ser 195 200 205 Glu Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu

Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe Val Arg Ala 275 280 285

Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn 290 295 300

Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro 305 310 315 320

Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr 325 330 335

Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln 340

<210> 152 <211> 307

<211> 307 <212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN

<222> 1-307

<223>

<400> 152

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys 1 5 10 15

Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp 25 30

Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser 35 40 45

Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala 50 55 60

Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro 65 70 75 80

Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg 85 90 95

Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Glu Gln Ala Gln Glu Gln 100 $$ 105 $$ 110

Gln Tyr Val Glu Gly Gly Gly Gly Ser Pro Gly Gly Gly Ser Gly Gly 115 120 125

Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln 130 135 140

Ser Phe Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp 145 150 155 160

Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His

Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala

Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 195 200 205

Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 210 215 220

Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln 225 230 230 235

Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu

Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala

260 265 270

Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser 275 280 285

His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 290 295 300

Ala Gln Pro 305

<210> 153

<211> 244 <212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN

<222> 1-244

<223>

<400> 153

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys 1 5 10 15

Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp 20 25 30

Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser 35 40 45

Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala 50 55 60

Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro 65 70 75 80

Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg 85 90 95

Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
100 105 110

Gln Tyr Val Glu Gly Gly Gly Gly Ser Pro Gly Gly Gly Ser Gly Gly 115 120 125

Gly Ser Asn Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His 130 135 140

His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn 145 150 155 160

Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn 165 170 175

Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly 180 185 190

Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr 195 200 205

Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln 210 215 220

Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala 225 230 235 240

Gln Glu Gln Gln

<210> 154

<211> 322

<212> PRT

<213> Artificial Sequence

<220>
<221> MUTAGEN
<222> 1-322
<223>
<400> 154

Met Ala Asp Cvs 5

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys 1 5 10 15

Arg Pro Pro Ala Pro Leu Leu Asp Pro As
n Asn Leu As
p Glu Asp $20 \hspace{1.5cm} 25 \hspace{1.5cm} 30 \hspace{1.5cm}$

Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser 35 40 45

Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala 50 60

Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro 65 70 75 80

Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg 85 90 95

Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
100 105 110

Gln Tyr Val Ile Glu Gly Gly Gly Ser Pro Gly Glu Pro Ser Gly Pro 115 120 125

Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 130 135 140

Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser 145 150 155 160

Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly 165 170 175

Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 180 185 190

Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 195 200 205

Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 210 215 220

Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 225 230 235 240

Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu
245 250 255

Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu 260 265 270

Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe 275 280 285

Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His 290 295 300

Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala 305 310 315 320

Gln Pro

<210> 155 <211> 259 <212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN <222> 1-259 <223> <400> 155 Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro 65 70 75 80 Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln Tyr Val Glu Gly Gly Gly Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 135 Pro Asn Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala 215 Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln <210> 156 <211> 322 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-322 <223> <400> 156 Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu 10 Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala

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Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu

40 45 Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gly Leu 65 70 75 80His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val 105 Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Tyr Val Glu Gly Gly Gly Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu 215 Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu 230 235 Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln <210> <211> 322 <212> PRT Artificial Sequence <213> <220> MUTAGEN <221> <222> 1-322 <223> <400> Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala

Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu

Leu Val 50	Leu	Leu	Gly	His	Ser 55	Leu	Gly	Ile	Pro	Trp 60	Ala	Pro	Leu	Ser
Ser Cys 65	Pro	Ser	Gln	Ala 70	Leu	Gln	Leu	Ala	Gly 75	Cys	Leu	Ser	Gly	Leu 80
His Ser	Gly	Leu	Phe 85	Leu	Tyr	Gln	Gly	Leu 90	Leu	Gln	Ala	Leu	Glu 95	Gly
Ile Ser	Pro	Glu 100	Leu	Gly	Pro	Thr	Leu 105	Asp	Thr	Leu	Gln	Leu 110	Asp	Val
Ala Asp	Phe 115	Ala	Thr	Thr	Ile	Trp 120	Gln	Gln	Met	Glu	Glu 125	Leu	Gly	Met
Ala Pro 130	Ala	Leu	Gln	Pro	Thr 135	Gln	Gly	Ala	Met	Pro 140	Ala	Phe	Ala	Ser
Ala Phe 145	Gln	Arg	Arg	Ala 150	Gly	Gly	Val	Leu	Val 155	Ala	Ser	His	Leu	Gln 160
Ser Phe	Leu	Glu	Val 165	Ser	Tyr	Arg	Val	Leu 170	Arg	His	Leu	Ala	Gln 175	Pro
Tyr Val	Glu	Gly 180	Gly	Gly	Gly	Ser	Pro 185	Gly	Glu	Pro	Ser	Gly 190	Pro	Ile
Ser Thr	Ile 195	Asn	Pro	Ser	Pro	Pro 200	Ser	Lys	Glu	Ser	His 205	Lys	Ser	Pro
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Lys Arg 225	Pro	Pro	Ala	Pro 230	Leu	Leu	Asp	Pro	Asn 235	Asn	Leu	Asn	Asp	Glu 240
Asp Val	Ser	Ile	Leu 245	Met	Asp	Arg	Asn	Leu 250	Arg	Leu	Pro	Asn	Leu 255	Glu
Ser Phe	Val	Arg 260	Ala	Val	Lys	Asn	Leu 265	Glu	Asn	Ala	Ser	Gly 270	Ile	Glu
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Pro Ser 290	Arg	His	Pro	Ile	Ile 295	Ile	Lys	Ala	Gly	Asp 300	Trp	Gln	Glu	Phe
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Leu Gln	Glu 35	Lys	Leu	Cys	Ala	Thr 40	Tyr	Lys	Leu	Cys	His 45	Pro	Glu	Glu

Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser 55 Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gly Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Tyr Val Glu Gly Gly Gly Ser Pro Gly Gly Gly Ser Gly Gly Gly 185 Ser Asn Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp 215 Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu 280 Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln 295 Glu Gln Gln 305 <210> 159 <211> 307 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-307 <223> <400> Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu 10 Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gly Leu

65 70 75 His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser 135 Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro Tyr Val Glu Gly Gly Gly Ser Pro Gly Gly Gly Ser Gly Gly Gly 185 Ser Asn Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala $260 \hspace{1.5cm} 265 \hspace{1.5cm} 265 \hspace{1.5cm} 270 \hspace{1.5cm}$ Ala Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln 305 <210> 160 <211> 128 <212> PRT <213> Human <400> Met Ala Pro Ala Arg Ser Pro Ser Pro Ser Thr Gln Pro Trp Glu His Val Asn Ala Ile Gln Glu Ala Arg Arg Leu Leu Asn Leu Ser Arg Asp Thr Ala Ala Glu Met Asn Glu Thr Val Glu Val Ile Ser Glu Met Phe Asp Leu Gln Glu Pro Thr Cys Leu Gln Thr Arg Leu Glu Leu Tyr Lys Gln Gly Leu Arg Gly Ser Leu Thr Lys Leu Lys Gly Pro Leu Thr Met 65 70 75 80Met Ala Ser His Tyr Lys Gln His Cys Pro Pro Thr Pro Glu Thr Ser Cys Ala Thr Gln Ile Ile Thr Phe Glu Ser Phe Lys Glu Asn Leu Lys Asp Phe Leu Leu Val Ile Pro Phe Asp Cys Trp Glu Pro Val Gln Glu

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Ser Cys Pro 65	o Ser Glr	Ala Lei 70	ı Gln	Leu	Ala	Gly 75	Cys	Leu	Ser	Gln	Leu 80
His Ser Gl	y Leu Phe 85	e Leu Ty:	c Gln	Gly	Leu 90	Leu	Gln	Ala	Leu	Glu 95	Gly
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Leu Gln Gl 35	ı Lys Lev	Cys Ala	a Thr 40	Туг	Lys	Leu	Cys	His 45	Pro	Glu	Glu
Leu Val Le	ı Leu Gly	His Se	. Leu	Gly	Ile	Pro	Trp 60	Ala	Pro	Leu	Ser
Ser Cys Pro 65	o Ser Glr	Ala Lei 70	ı Gln	Leu	Ala	Gly 75	Cys	Leu	Ser	Gln	Leu 80
His Ser Gl	y Leu Phe 85	Leu Ty:	Gln	Gly	Leu 90	Leu	Gln	Ala	Leu	Glu 95	Gly
Ile Ser Pro	o Glu Leu 100	Gly Pro	Thr	Leu 105	Asp	Thr	Leu	Gln	Leu 110	Asp	Val
Ala Asp Pho		Thr Ile	120	Gln	Gln	Met	Glu	Glu 125	Leu	Gly	Met
Ala Pro Ala 130	a Leu Glr	Pro Th:		Gly	Ala	Met	Pro 140	Ala	Phe	Ala	Ser

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136/348

105

100

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Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala
Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
                               105
Gln Tyr Val Glu Gly Gly Gly Ser Pro Gly Gly Gly Ser Gly Gly 115 120 125
Gly Ser Asn Met Ala Ser Pro Ala Pro Pro Ala Cys Asp Leu Arg Val
Leu Ser Lys Leu Leu Arg Asp Ser His Val Leu His Ser Arg Leu Ser
Gln Cys Pro Glu Val His Pro Leu Pro Thr Pro Val Leu Leu Pro Ala
Val Asp Phe Ser Leu Gly Glu Trp Lys Thr Gln Met Glu Glu Thr Lys
                                185
Ala Gln Asp Ile Leu Gly Ala Val Thr Leu Leu Leu Glu Gly Val Met
Ala Ala Arg Gln Gln Leu Gly Pro Thr Cys Leu Ser Ser Leu Leu Gly
Gln Leu Ser Gly Gln Val Arg Leu Leu Leu Gly Ala Leu Gln Ser Leu
Leu Gly Thr Gln Leu Pro Pro Gln Gly Arg Thr Thr Ala His Lys Asp
Pro Asn Ala Ile Phe Leu Ser Phe Gln His Leu Leu Arg Gly Lys Val
Arg Phe Leu Met Leu Val Gly Gly Ser Thr Leu Cys Val Arg
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Ser Leu Gly Glu Trp Lys Thr Gln Met Glu Glu Thr Lys Ala Gln Asp 50 60

Ile Leu Gly Ala Val Thr Leu Leu Leu Glu Gly Val Met Ala Ala Arg 65 70 75 80

Gln Gln Leu Gly Pro Thr Cys Leu Ser Ser Leu Leu Gly Gln Leu Ser 85 90 95

Gly Gln Val Arg Leu Leu Gly Ala Leu Gln Ser Leu Leu Gly Thr

Gln Leu Pro Pro Gln Gly Arg Thr Thr Ala His Lys Asp Pro Asn Ala 115 120 125

Ile Phe Leu Ser Phe Gln His Leu Leu Arg Gly Lys Val Arg Phe Leu 130 135 140

Met Leu Val Gly Gly Ser Thr Leu Cys Val Arg Tyr Val Ile Glu Gly 145 150 155 160

Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly Gly Ser Asn Met Ala Asn 165 170 175

Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro 180 \$190\$

Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile 195 200 205

Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe Val Arg 210 215 220

Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg 225 230 235 240

Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His 245 250 255

Pro Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu 260 265 270

Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln 275 280 285

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Glu Val His Pro Leu Pro Thr Pro Val Leu Leu Pro Ala Val Asp Phe 35 40 45

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Ile Leu Gly Ala Val Thr Leu Leu Leu Glu Gly Val Met Ala Ala Arg
Gln Gln Leu Gly Pro Thr Cys Leu Ser Ser Leu Leu Gly Gln Leu Ser
Gly Gln Val Arg Leu Leu Gly Ala Leu Gln Ser Leu Leu Gly Thr
Gln Leu Pro Pro Gln Gly Arg Thr Thr Ala His Lys Asp Pro Asn Ala
Ile Phe Leu Ser Phe Gln His Leu Leu Arg Gly Lys Val Arg Phe Leu
                        135
Met Leu Val Gly Gly Ser Thr Leu Cys Val Arg Glu Phe His Ala Tyr
                    150
Val Glu Gly Gly Gly Ser Pro Gly Gly Gly Ser Gly Gly Ser 165 Pro Gly Gly Gly Ser 175 175
Asn Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu
                               185
Lys Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu
                            200
Asp Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu
               215
Ala Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu
Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala
Pro Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe
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Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu
Gln Gln
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His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu

295

Ala Gln Pro 305 300

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Gln	Asp	Ile 35	Leu	Met	Glu	Asn	Asn 40	Leu	Arg	Arg	Pro	Asn 45	Leu	Glu	Ala
Phe	Asn 50	Arg	Ala	Val	Lys	Ser 55	Leu	Gln	Asn	Ala	Ser 60	Ala	Ile	Glu	Ser
Ile 65	Leu	Lys	Asn	Leu	Leu 70	Pro	Cys	Leu	Pro	Leu 75	Ala	Thr	Ala	Ala	Pro 80
Thr	Arg	His	Pro	Ile 85	His	Ile	Lys	Asp	Gly 90	Asp	Trp	Asn	Glu	Phe 95	Arg
Arg	Lys	Leu	Thr 100	Phe	Tyr	Leu	Lys	Thr 105	Leu	Glu	Asn	Ala	Gln 110	Ala	Gln
Gln	Tyr	Val 115	Ile	Glu	Gly	Arg	Ile 120	Ser	Pro	Gly	Glu	Pro 125	Ser	Gly	Pro
Ile	Ser 130	Thr	Ile	Asn	Pro	Ser 135	Pro	Pro	Ser	Lys	Glu 140	Ser	His	Lys	Ser
Pro 145	Asn	Met	Ala	Thr	Pro 150	Leu	Gly	Pro	Ala	Ser 155	Ser	Leu	Pro	Gln	Ser 160
Phe	Leu	Leu	Lys	Cys 165	Leu	Glu	Gln	Val	Arg 170	Lys	Ile	Gln	Gly	Asp 175	Gly
Ala	Ala	Leu	Gln 180	Glu	Lys	Leu	Cys	Ala 185	Thr	Tyr	Lys	Leu	Cys 190	His	Pro
Glu	Glu	Leu 195	Val	Leu	Leu	Gly	His 200	Ser	Leu	Gly	Ile	Pro 205	Trp	Ala	Pro
Leu	Ser 210	Ser	Cys	Pro	Ser	Gln 215	Ala	Leu	Gln	Leu	Ala 220	Gly	Cys	Leu	Ser
Gln 225	Leu	His	Ser	Gly	Leu 230	Phe	Leu	Tyr	Gln	Gly 235	Leu	Leu	Gln	Ala	Leu 240
Glu	Gly	Ile	Ser	Pro 245	Glu	Leu	Gly	Pro	Thr 250	Leu	Asp	Thr	Leu	Gln 255	Leu
Asp	Val	Ala	Asp 260	Phe	Ala	Thr	Thr	Ile 265	Trp	Gln	Gln	Met	Glu 270	Glu	Leu
Gly	Met	Ala 275	Pro	Ala	Leu	Gln	Pro 280	Thr	Gln	Gly	Ala	Met 285	Pro	Ala	Phe
Ala	Ser 290	Ala	Phe	Gln	Arg	Arg 295	Ala	Gly	Gly	Val	Leu 300	Val	Ala	Ser	His
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Gln	Pro														

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Gln	Asp	Ile 35	Leu	Met	Glu	Asn	Asn 40	Leu	Arg	Arg	Pro	Asn 45	Leu	Glu	Ala
Phe	Asn 50	Arg	Ala	Val	Lys	Ser 55	Leu	Gln	Asn	Ala	Ser 60	Ala	Ile	Glu	Ser
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Thr	Arg	His	Pro	Ile 85	His	Ile	Lys	Asp	Gly 90	Asp	Trp	Asn	Glu	Phe 95	Arg
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Leu	Glu	Gln 195	Val	Arg	Lys	Ile	Gln 200	Gly	Asp	Gly	Ala	Ala 205	Leu	Gln	Glu
Lys	Leu 210	Cys	Ala	Thr	Tyr	Lys 215	Leu	Cys	His	Pro	Glu 220	Glu	Leu	Val	Leu
Leu 225	Gly	His	Ser	Leu	Gly 230	Ile	Pro	Trp	Ala	Pro 235	Leu	Ser	Ser	Cys	Pro 240
Ser	Gln	Ala	Leu	Gln 245	Leu	Ala	Gly	Сув	Leu 250	Ser	Gln	Leu	His	Ser 255	Gly
Leu	Phe	Leu	Tyr 260	Gln	Gly	Leu	Leu	Gln 265	Ala	Leu	Glu	Gly	Ile 270	Ser	Pro
Glu	Leu	Gly 275	Pro	Thr	Leu	Asp	Thr 280	Leu	Gln	Leu	Asp	Val 285	Ala	Asp	Phe
	Thr 290	Thr	Ile	Trp	Gln	Gln 295	Met	Glu	Glu	Leu	Gly 300	Met	Ala	Pro	Ala
Leu 305	Gln	Pro	Thr	Gln	Gly 310	Ala	Met	Pro	Ala	Phe 315	Ala	Ser	Ala	Phe	Gln 320
Arg	Arg	Ala	Gly	Gly 325	Val	Leu	Val	Ala	Ser 330	His	Leu	Gln	Ser	Phe 335	Leu
Glu	Val	Ser	Tyr	Arg	Val	Leu	Arg	His	Leu	Ala	Gln	Pro			

340 345

<210> 181

<211> 307 <212> PRT

<212> PRT <213> Artificial Sequence

<220>

<221> MUTAGEN

<222> 1-307

<223>

<400> 183

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 1 5 10 15

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Ser Glu Asp 20 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 100 105 110

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly
115 120 125

Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln 130 135 140

Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp 145 150 150 155 160

Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His 165 170 175

Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 180 185 190

Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 195 200 205

Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 210 215 220

Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln 225 230 235 240

Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu 245 250 255

Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 260 265 270

Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser 275 280 285

His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu

Ala Gln Pro

305

<210> 182 <211> 322

<212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-322 <400> 182 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Ser Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80 Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser 150 155 Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly 165 170 175 Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 200 Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 215 Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu 265 Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe 280 Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 349 <211> <212> PRT

<213> Artificial Sequence <220> MUTAGEN <221> <222> 1-349 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Ser Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 40 Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu 200 Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu 215 Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro 265 Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala 295 Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln 315 Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu 330 Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 184

<211> <212> <213>	307 PRT Artificia	. Sequence					
<220> <221> <222> <223>	MUTAGEN 1-307						
<400>	184						
Met Ala	Asn Cys Se 5	Asn Met I	Ile Asp	Glu Ile 10	Ile Thr	His Le	_
Gln Pro	Pro Leu Pr 20	Leu Leu A	Asp Phe 25	Asn Asn	Leu Asn	Ile Gl 30	u Asp
Gln Asp	Ile Leu Me 35		Asn Leu 10	Arg Arg	Pro Asr 45	Leu Gl	u Ala
Phe Asr 50	Arg Ala Va	Lys Ser L 55	Leu Gln	Asn Ala	Ser Ala	lle Gl	u Ser
Ile Leu 65	Lys Asn Le	ı Leu Pro C 70	Cys Leu	Pro Leu 75	Ala Thr	Ala Al	a Pro 80
Thr Arg	His Pro Il 85	e His Ile I	Lys Asp	Gly Asp 90	Trp Asr	Glu Ph 95	
Arg Lys	Leu Thr Ph 100	e Tyr Leu I	Lys Thr 105	Leu Glu	Asn Ala	Gln Al 110	a Gln
Gln Tyr	Val Ile Gl		le Ser L20	Pro Gly	Gly Gly 125		y Gly
Gly Ser 130	Asn Met Al	a Thr Pro I 135	Leu Gly	Pro Ala	Ser Ser 140	Leu Pr	o Gln
Ser Phe	Leu Leu Ly	S Cys Leu G 150	Glu Gln	Val Arg 155	Lys Ile	Gln Gl	y Asp 160
Gly Ala	Ala Leu Gl		Leu Cys	Ala Thr 170	Tyr Lys	Leu Cy 17	
Pro Glu	Glu Leu Va 180	l Leu Leu G	Gly His 185	Ser Leu	Gly Ile	Pro Tr 190	p Ala
Pro Leu	Ser Ser Cy 195		31n Ala 200	Leu Gln	Leu Ala 205		s Leu
Ser Glr 210	Leu His Se	Gly Leu F 215	Phe Leu	Tyr Gln	Gly Leu 220	Leu Gl	n Ala
Leu Glu 225	Gly Ile Se	Pro Glu L 230	Seu Gly	Pro Thr 235	Leu Asp	Thr Le	u Gln 240
Leu Asp	Val Ala As 24		thr Thr	Ile Trp 250	Gln Gln	Met Gl 25	
Leu Gly	Met Ala Pro 260	o Ala Leu G	Eln Pro 265	Thr Gln	Gly Ala	Met Pr 270	o Ala
Phe Ala	Ser Ala Pho 275		Arg Ala 280	Gly Gly	Val Leu 285		a Ser
His Leu 290	Gln Ser Ph	e Leu Glu V 295	al Ser	Tyr Arg	Val Leu 300	Arg Hi	s Leu
Ala Gln 305	Pro						
<210> <211> <212> <213>	185 322 PRT Artificia	Sequence					

<220> <221> MUTAGEN 1-322 <400> 185 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Ile Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 55 Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 185 Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe 280 Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 186 <211> 349 <212> PRT Artificial Sequence

<220>

<221>

MUTAGEN

<222> 1-349 <223> <400> 186 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 10 Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Ile Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu 215 Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro 235 Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 280 Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu 330 Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 187 <211> <212> PRT

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Artificial Sequence

<213>

<220> <221> MUTAGEN <222> 1-307 <223> <400> 187 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Leu Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 40 Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln 135 Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp 145 150 150 4155 160 Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 185 Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 200 Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu 250 Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser 280 His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 295 Ala Gln Pro 305 <210> 188 <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-322

<223>

<400>

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Leu Glu Asp

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro

Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro

Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 135

Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser

Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly

Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro

Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 200

Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser

Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu

Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu

Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu

Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe

Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His

Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala

Gln Pro

<210> 189

<211> 349

<212> PRTArtificial Sequence <213>

<220>

MUTAGEN <221>

1-349 <222>

<223>

<400> 189

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Leu Glu Asp 20 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 55 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 100 105 110

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala 115 120 125

Ser Glu Gly Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser 145 150 155 160

Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr 165 170 175

Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser 180 185 190

Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu 195 200 205

Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu 210 215 220

Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro 225 230 235 240

Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly

Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro 260 265 270

Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 275 280 285

Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala 290 295 300

Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln 305 310 315 320

Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu 325 330 335

Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 340 345

<210> 190

<211> 307 <212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN

1-307 <222> <223> <400> 190 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Met Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 40 Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 90 Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 115 120 125 Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His 170 Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 215 Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 265 Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 295 Ala Gln Pro 305 <210> 191 <211> 322 <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN

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<222>

<223> <400> 1-322

191

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Met Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 90 Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 200 Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 215 Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala 315 Gln Pro <210> 192 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-349 <223> <400> 192

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 10 Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Met Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala Ser Glu Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala 295 Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln 315 Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 345 <210> 193 307 <211> <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-307 <223>

<400> 193

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Tyr Glu Asp

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 55

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro

Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly

Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln

Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp

Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His

Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 185

Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu

Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala

Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln

Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu

Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala

Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser 280

His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu

Ala Gln Pro

<210> 194

<211> 322

<212> Artificial Sequence <213>

<220>

<221> MUTAGEN

1-322 <222>

<223>

<400> 194

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Tyr Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 135 Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 230 Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe 280 Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 195 <211> 349 <21.2> PRT <213> Artificial Sequence <220> MUTAGEN <221> <222> 1-349 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 1 $$ 5 $$ 10 $$ 15

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10 15 Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Ala Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 120 Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln 135 Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 185 Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 200 Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 295 Ala Gln Pro <210> 197 <211> <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-322 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 10 Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Ala Glu Asp

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 120 Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 135 Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 230 235 Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu 250 Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His 295 Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 198 <211> 349 <212> PRT Artificial Sequence <220> MUTAGEN <221> <222> 1-349 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Ala Glu Asp

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Val Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 55 Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 185 Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe 280 Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His 295 Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 201 <211> 349 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-349 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Val Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser 185 Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys·Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 280 Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala 295 Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 202 <21.1> 307 <212> PRT Artificial Sequence <220> MUTAGEN <221> <222> 1-307 <223> <400> 202 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala

45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 55 Leu Pro Leu Ala Thr Ala Ala Pro

40

65 70 75 80

Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 100 \$105\$

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly
115 120 125

Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln 130 135 140

Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp 145 150 150 155 160

Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His 165 170 175

Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 180 185 190

Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 195 200 205

Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 210 215 220

Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln 225 230 235 240

Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu 245 250 255

Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 260 265 270

Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser 275 280 285

His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 290 295 300

Ala Gln Pro 305

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Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 55 60

Ile 65	Leu	Lys	Asn	Leu	Leu 70	Pro	Cys	Leu	Pro	Leu 75	Ala	Thr	Ala	Ala	Pro 80
Thr	Arg	His	Pro	Ile 85	His	Ile	Lys	Asp	Gly 90	Asp	Trp	Asn	Glu	Phe 95	Arg
Arg	Lys	Leu	Thr 100	Phe	Tyr	Leu	Lys	Thr 105	Leu	G1u	Asn	Ala	Gln 110	Ala	Gln
Gln	Tyr	Val 115	Ile	Glu	Gly	Arg	Ile 120	Ser	Pro	Gly	Glu	Pro 125	Ser	Gly	Pro
Ile	Ser 130	Thr	Ile	Asn	Pro	Ser 135	Pro	Pro	Ser	Lys	Glu 140	Ser	His	Lys	Ser
Pro 145	Asn	Met	Ala	Thr	Pro 150	Leu	Gly	Pro	Ala	Ser 155	Ser	Leu	Pro	Gln	Ser 160
Phe	Leu	Leu	Lys	Cys 165	Leu	Glu	Gln	Val	Arg 170	Lys	Ile	G1n	Gly	Asp 175	Gly
Ala	Ala	Leu	Gln 180	G1u	Lys	Leu	Cys	Ala 185	Thr	Tyr	Lys	Leu	Cys 190	His	Pro
Glu	Glu	Leu 195	Val	Leu	Leu	Gly	His 200	Ser	Leu	Gly	Ile	Pro 205	Trp	Ala	Pro
Leu	Ser 210	Ser	Cys	Pro	Ser	Gln 215	Ala	Leu	Gln	Leu	Ala 220	Gly	Cys	Leu	Ser
Gln 225	Leu	His	Ser	Gly	Leu 230	Phe	Leu	туг	Gln	Gly 235	Leu	Leu	Gln	Ala	Leu 240
Glu	Gly	Ile	Ser	Pro 245	Glu	Leu	Gly	Pro	Thr 250	Leu	Asp	Thr	Leu	Gln 255	Leu
Asp	Val	Ala	Asp 260	Phe	Ala	Thr	Thr	Ile 265	Trp	G1n	Gln	Met	Glu 270	Glu	Leu
Gly	Met	Ala 275	Pro	Ala	Leu	Gln	Pro 280	Thr	Gln	Gly	Ala	Met 285	Pro	Ala	Phe
Ala	Ser 290	Ala	Phe	Gln	Arg	Arg 295	Ala	Gly	Gly	Val	Leu 300	Val	Ala	Ser	His
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Gln	Pro														
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Gln	Asp	Ile 35	Leu	Met	Glu	Asn	Asn 40	Leu	Arg	Arg	Pro	Asn 45	Leu	Glu	Ala
Phe	Asn 50	Arg	Ala	Val	Lys	Ser 55	Leu	Gln	Asn	Ala	Ser 60	Ala	Ile	Glu	Ser

Ile Leu L 65	ys Asn	Leu	Leu 70	Pro	Cys	Leu	Pro	Leu 75	Ala	Thr	Ala	Ala	Pro 80
Thr Arg H	lis Pro	Ile 85	His	Ile	Lys	Asp	Gly 90	Asp	Trp	Asn	Glu	Phe 95	Arg
Arg Lys L	eu Thr 100	Phe	Tyr	Leu	Lys	Thr 105	Leu	Glu	Asn	Ala	Gln 110	Ala	Gln
Gln Tyr V 1	al Ile .15	Glu	Gly	Arg	Ile 120	Ser	Pro	Gln	Pro	Pro 125	Val	Asn	Ala
Gly Gly G 130	ly Ser	Gly	Gly	Gly 135	Ser	Gly	Gly	Gly	Ser 140	Glu	Gly	Gly	G1y
Ser Glu G 145	ly Gly	Gly	Ser 150	Glu	Gly	Gly	Gly	Ser 155	Glu	Gly	Gly	Gly	Ser 160
Gly Gly G	Sly Ser	Gly 165	Ser	Gly	Asp	Phe	Asp 170	Tyr	Glu	Asn	Met	Ala 175	Thr
Pro Leu G	ly Pro	Ala	Ser	Ser	Leu	Pro 185	Gln	Ser	Phe	Leu	Leu 190	Lys	Ser
Leu Glu G 1	ln Val .95	Arg	Lys	Ile	Gln 200	Gly	Asp	Gly	Ala	Ala 205	Leu	Gln	Glu
Lys Leu C 210	ys Ala	Thr	Tyr	Lys 215	Leu	Cys	His	Pro	Glu 220	Glu	Leu	Val	Leu
Leu Gly H 225	lis Ser	Leu	Gly 230	Ile	Pro	Trp	Ala	Pro 235	Leu	Ser	Ser	Cys	Pro 240
Ser Gln A	la Leu	Gln 245	Leu	Ala	Gly	Cys	Leu 250	Ser	Gln	Leu	His	Ser 255	Gly
Leu Phe I	eu Tyr 260	Gln	Gly	Leu	Leu	Gln 265	Ala	Leu	Glu	Gly	Ile 270	Ser	Pro
Glu Leu G 2	ly Pro 275	Thr	Leu	Asp	Thr 280	Leu	Gln	Leu	Asp	Val 285	Ala	Asp	Phe
Ala Thr T 290	hr Ile	Trp	Gln	Gln 295	Met	Glu	Glu	Leu	Gly 300	Met	Ala	Pro	Ala
Leu Gln F 305	ro Thr	Gln	Gly 310	Ala	Met	Pro	Ala	Phe 315	Ala	Ser	Ala	Phe	Gln 320
Arg Arg A	la Gly	Gly 325	Val	Leu	Val	Ala	Ser 330	His	Leu	Gln	Ser	Phe 335	Leu
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Gln Pro P	ro Leu 20	Pro	Leu	Leu	Asp	Phe 25	Asn	Asn	Leu	Asn	Gly 30	Glu	Asp
Met Asp I	le Leu 5	Met	Glu	Asn	Asn 40	Leu	Arg	Arg	Pro	Asn 45	Leu	Glu	Ala
Phe Asn A	rg Ala	Val	Lys	Ser	Leu	Gln	Asn	Ala	Ser	Ala	Ile	Glu	Ser

50 55 60 Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 120 Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln 135 Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 185 Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln 235 Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu 250 Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 295 Ala Gln Pro 305 <210> 206 <211> 322 <212> PRT <213> Artificial Sequence <220> MUTAGEN <221> <222> 1-322 <223> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Met Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser

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Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro

Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly 165 170 Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 185 Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 195 200 205 Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe 280 Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His 295 Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 207 <211> 349 <212> PRT Artificial Sequence <220> <221> MUTAGEN <222> 1-349 <400> 207 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Met Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 40 Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro

Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 90 Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 100 $$105\$ Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala Ser Glu Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu 210 215 220Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 280 Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 208 <211> 307 <212> PRT Artificial Sequence <213> <220> MUTAGEN <221> <222> 1-307 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 10 Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Asn Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro

70 75 Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln 135 Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu 250 Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 265 Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 305 <210> 209 <211> 322 <212> PRT <213> Artificial Sequence <220> MUTAGEN <221> <222> 1-322 <223> 209 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 25 Asn Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 100 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 120 Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 135 Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 230 235 Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His 295 Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 210 <211> 349 <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-349 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Asn Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala 120 Gly Gly Gly Ser Gly Gly Ser Gly Gly Ser Glu Gly Gly Gly 135 Ser Glu Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala 295 Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 211 <211> 307 <212> PRT <213> Artificial Sequence <220> MUTAGEN <221> <222> 1-307 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Ser Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg

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WO 01/76639 85 90 95 Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln 135 Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp 150 155 Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 200 Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 215 Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 265 Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 305 <21.0> 212 <211> 322 <212> PRT

Artificial Sequence <213>

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Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp

Gln Ser Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro

Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln

105 110 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 120 Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 135 Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 200 Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 215 Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu 265 Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe 280 Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His 295 Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala 315 Gln Pro <210> 213 <211> 349 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-349 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Ser Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala 120 Gly Gly Gly Ser Gly Gly Ser Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu 215 Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro 265 Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 280 Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu 330 Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 214 <211> 307 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN 1-307 <222> <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 10 Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Gln Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 120 Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln 135 Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 185 Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 200 Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 295 300 Ala Gln Pro <210> 215 <211> 322 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-322 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Gln Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 90 Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 120 Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 135 Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 185 Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 200 Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His 295 Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala 315 310 Gln Pro <210> 216 <211> 349 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-349 <223> <400> 216 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 10 Gln Gln Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala

120 115 Ser Glu Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 217 <211> 307 <212> PRT <213> Artificial Sequence <220> MUTAGEN <221> <222> 1-307 <223> <400> 217 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 25 Gln His Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 40 Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg

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Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 120 Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His 165 170 175Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 200 Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 305 <210> 218 <211> 322 <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-322 <223> <400> 218 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln His Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 90 Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro

Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 135 Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser 150 155 Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly 170 Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 230 Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu 265 Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 219 <211> 349 <212> PRT <213> Artificial Sequence <220> MUTAGEN <221> <222> 1-349 <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln His Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 40 Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Glu Gly Gly

130 135 140 Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu 200 Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 220 <211> 307 <212> Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-307 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 10 Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Val Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 115 120 125

Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 215 Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 221 <210> <211> 322 Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-322 <223> <400> 221 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 10 Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Val Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 55 Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser

Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly 170 Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 185 Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His 295 Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 222 349 <211> <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-349 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 10 Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Val Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 90 Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala 120 Ser Glu Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser

145				150					155					160
Gly Gly	Gly	Ser	Gly 165	Ser	Gly	Asp	Phe	Asp 170	Tyr	Glu	Asn	Met	Ala 175	Thr
Pro Leu	Gly	Pro 180	Ala	Ser	Ser	Leu	Pro 185	Gln	Ser	Phe	Leu	Leu 190	Lys	Ser
Leu Glu	Gln 195	Val	Arg	Lys	Ile	Gln 200	Gly	Asp	Gly	Ala	Ala 205	Leu	G1.n	Glu
Lys Leu 210	Cys	Ala	Thr	Tyr	Lys 215	Leu	Cys	His	Pro	Glu 220	Glu	Leu	Val	Leu
Leu Gly 225	His	Ser	Leu	Gly 230	Ile	Pro	Trp	Ala	Pro 235	Leu	Ser	Ser	Cys	Pro 240
Ser Gln	Ala	Leu	Gln 245	Leu	Ala	Gly	Cys	Leu 250	Ser	Gln	Leu	His	Ser 255	Gly
Leu Phe	Leu	Туг 260	Gln	Gly	Leu	Leu	Gln 265	Ala	Leu	Glu	Gly	Ile 270	Ser	Pro
Glu Leu	Gly 275	Pro	Thr	Leu	Asp	Thr 280	Leu	Gln	Leu	Asp	Val 285	Ala	Asp	Phe
Ala Thr 290	Thr	Ile	Trp	Gln	Gln 295	Met	Glu	Glu	Leu	Gly 300	Met	Ala	Pro	Ala
Leu Gln 305	Pro	Thr	Gln	Gly 310	Ala	Met	Pro	Ala	Phe 315	Ala	Ser	Ala	Phe	Gln 320
Arg Arg	Ala	Gly	Gly 325	Val	Leu	Val	Ala	Ser 330	His	Leu	Gln	Ser	Phe 335	Leu
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Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln 235 Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 295 Ala Gln Pro <210> 224 322 <211> <212> PRT <213> Artificial Sequence <220> MUTAGEN <221> <222> 1-322 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Asp Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 120 Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser

145 150 155 160 Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 215 Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe 280 Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 225 <210> <211> 349 <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-349 <223> <400> 225 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Asp Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 40 Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 90 Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser

Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Fro Gln Ser Phe Leu Leu Lys Ser ુ 185 Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln 305 $$ 310 $$. 315 $$ 320 Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 226 <211> 307 <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-307 <223> <400> 226 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 10 Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Asp Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln

Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp 150 155 Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 305 <210> 227 <211> 322 <212> PRT Artificial Sequence <213> <220> MUTAGEN <221> <222> 1-322 <223> <400> 227 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 25 Gln Asp Ile Leu Met Asp Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 120 Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 135 1.40 Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser

Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly 165 170 Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 185 Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 230 Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe 280 Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 228 <211> 349 <212> PRTArtificial Sequence <220> <221> MUTAGEN <222> 1-349 <223> <400> 228 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 10 Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Asp Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala 120 Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser

Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr 170 Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser 185 Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala 295 Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 229 <211> 307 <212> PRT Artificial Sequence <220> MUTAGEN <221> <222> 1-307 <223> <400> 229 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Pro Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 120 Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp

150 145 155 160 Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His 170 Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 200 Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 215 Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 265 Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 305 230 <210> <211> 322 <212> <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-322 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Pro Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95 Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 120 Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 135 Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser

Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 185 Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 200 Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu 265 Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His 295 Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 231 <211> 349 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-349 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 10 Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Pro Asn Leu Arg Arg Pro Asn Leu Glu Ala 40 Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala 120 Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Gly Gly 130 135 140 Ser Glu Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr

165 170 175 Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser 185 Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro 230 Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 280 Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala 295 Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 232 <211> 307 <212> PRT <213> Artificial Sequence <220> MUTAGEN <221> 1-307 <222> <223> <400> 232 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Arg Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln 135 Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp

Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His 170 Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 185 Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu 245 250 Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 295 Ala Gln Pro 305 <210> 233 <211> 322 <212> PRT Artificial Sequence <220> <221> MUTAGEN <222> 1-322 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Arg Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 120 Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser 150 Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly

165 170 175 Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 185 Glu Glu Leu Val Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 230 Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 234 <211> 349 <212> PRT Artificial Sequence <220> MUTAGEN <221> <222> 1-349 <223> <400> 234 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Arg Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala Ser Glu Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser

Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr

Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser 180 185 Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu 200 Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu 210 215 220 Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln 315 Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 235 <211> 307 <212> PRT<213> Artificial Sequence <220> <221> MUTAGEN <222> 1-307 <223> <400> 235 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu His Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 120 Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp

Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His 170 Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 185 Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu 250 Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 295 300 Ala Gln Pro 305 <210> 236 <211> 322 <212> PRTArtificial Sequence <220> MUTAGEN <221> <222> 1-322 <223> <400> 236 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu His Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser 155 Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly 170

Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 180 185 Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 200 Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His 295 Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 237 <211> 349 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-349 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 10 Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu His Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala 120 Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr

Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu 215 Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 280 Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 345 <210> 238 <211> 307 <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN _ 1-307 <222> <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 25 Gln Asp Ile Leu Met Glu Thr Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln 135 Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp 145 150 150 155 160 Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His

165 170 Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 185 Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 200 Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 210 215 220 Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 265 Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 305 <210> 239 <211> 322 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-322 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 10 Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Thr Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 120 Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 135

Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser

Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly

Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 185 Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 200 Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 215 Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His 295 Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala 310 315 Gln Pro <210> 240 <211> 349 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-349 <223> <400> 240 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 25 Gln Asp Ile Leu Met Glu Thr Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala 120 Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Gly Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser

190 185 180 Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly 250 Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala 295 Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 340 345 <210> 241 307 <211> <212> PRT Artificial Sequence <220> MUTAGEN <221> <222> 1-307 <223> <400> 241 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Pro Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 55 Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 115 120 125 Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His

Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 185 Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 200 Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 210 215 220 Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu 250 Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 265 Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 305 <210> 242 <211> 322 PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-322 <223> <400> 242 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 25 Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Pro Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 120 Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 135 Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro

185 190 180 Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 215 Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 230 Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro . <210> 243 349 <211> <212> PRT Artificial Sequence <220> MUTAGEN <221> <222> 1-349 <223> <400> 243 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 10 Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Pro Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 55 Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala Gly Gly Gly Ser Gly Gly Gly Gly Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ger Glu Gly Gly Gly Ser Glu Gly Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr 170

207/348

Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser 180 185 190

Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 280 Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala 295 Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 244 <211> 307 <212> PRT Artificial Sequence <220> MUTAGEN <221> <222> 1-307 <223> <400> 244 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Pro Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His

Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 185 Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 215 Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu 250 Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 265 Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 295 Ala Gln Pro <210> 245 <211> 322 <212> <213> Artificial Sequence <220> <221> MUTAGEN 1-322 <223> <400> 245 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 25 Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Pro Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 120 Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 135 Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro

185 190 180 Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 200 Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu 250 Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His 295 Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 246 <211> 349 <212> <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-349 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 25 Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Pro Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Gly Ser Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr

Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser

Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu 200 Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 280 Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala 295 Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 247 <211> 307 <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-307 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 40 Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Val Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 90 Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His

Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 185 Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 215 Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 295 Ala Gln Pro <210> 248 <211> 322 PRT <212> <213> Artificial Sequence <220> MUTAGEN <221> <222> 1-322 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 40 Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Val Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 135 Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 185

Glu Glu Leu Val Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 200 Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 230 Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu 265 Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe 280 Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 249 <211> 349 <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-349 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Val Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala 120 Gly Gly Gly Ser Gly Gly Gly Gly Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser

Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu 200 Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu 210 215 220Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 280 Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 250 <211> 307 <212> <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-307 <223> <400> 250 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 25 Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ala Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 120 Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln 135 Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala

185 190 180 Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser 280 His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> <211> 322 <212> PRT <213> Artificial Sequence <220> MUTAGEN <221> <222> 1-322 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ala Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 90 Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 120 Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser

Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly

Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 180 185 190

Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 200 Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 215 Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 252 <211> 349 <212> PRT <213> Artificial Sequence <220> MUTAGEN <221> <222> 1-349 <223> <400> 252 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 25 Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ala Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Glu Gly Gly Gly 135 Ser Glu Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser

Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu

200 195 Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro 265 Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 280 Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 253 <211> 307 <212> Artificial Sequence <220> <221> MUTAGEN <222> 1-307 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 10 Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Leu Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 120 Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His

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Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala

180

Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 200 Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln 230 Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser 280 His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 295 Ala Gln Pro <210> 254 <211> 322 <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-322 <223> <400> 254 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Leu Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 135 Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro

200 205 195 Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu 250 Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu 265 Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 255 <211> 349 <212> PRT <213> Artificial Sequence <220> MUTAGEN <221> <222> 1-349 <223> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 25 Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 40 Phe Asn Arg Ala Val Lys. Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Leu Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala 120 Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser

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185

Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu
195 200 205

Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu 215 Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 275 280 285Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala 295 Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln 315 Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 256 <211> 307 <212> PRT Artificial Sequence <220> <221> MUTAGEN <222> 1-307 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Trp Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 115 120 125 Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala

Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 200 Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 215 Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 265 Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 305 <210> 257 <211> 322 <212> PRT <213> Artificial Sequence <220> MUTAGEN <221> <222> 1-322 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Trp Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 185 Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro

200

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Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser
                       215
Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu
           · 230
                                       235
Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu
Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu
Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe
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Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His
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Gln Pro
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Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala
Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser
Ile Leu Lys Asn Leu Trp Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro
Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg
Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln
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Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala
Gly Gly Gly Ser Gly Gly Ser Gly Gly Ser Glu Gly Gly Gly
Ser Glu Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser
Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr
Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser
Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu
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Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu 215 Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro 225 230 235 240 Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 345 <210> 259 <211> 307 <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-307 <223> <400> 259 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Asp Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu

205 200 Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu 250 Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 265 Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 295 Ala Gln Pro 305 <210> 260 <211> 322 <212> PRT Artificial Sequence <220> <221> MUTAGEN <222> 1-322 <223> <400> 260 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 20 25 30Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Asp Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 120 Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly

Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro

Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro

Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 215 Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 230 Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe 280 Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 261 <211> 349 <212> PRT<213> Artificial Sequence <220> MUTAGEN <221> <222> 1-349 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 55 Ile Leu Lys Asn Leu Asp Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala Gly Gly Gly Ser Gly Gly Gly Gly Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu 200 Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu

220 215 210 Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro 265 Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 280 Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala 295 Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 262 <211> 307 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN 1-307 <222> <223> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Asn Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln 135 Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 185 Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu

Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 215 Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 295 Ala Gln Pro 305 <210> 263 <211> 322 PRT Artificial Sequence <212> <213> <220> MUTAGEN <221> <222> 1-322 <223> <400> 263 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 60Ile Leu Lys Asn Leu Asn Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 135 Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser 155 Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly 165 170 175 Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 200 Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser

215 220 210 Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu 265 Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe 280 Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 264 349 <211> <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-349 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Asn Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu 200

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Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu

Leu Gly His Ser Leu Gly Île Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Neu His Ser Gly 245 250 Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ite Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 280 Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 345 <210> 265 <211> 307 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-307 <223> <400> 265 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Glu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 185 Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 200

Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 215 Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln 230 235 Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser 280 His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 295 Ala Gln Pro <210> 266 322 <211> <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-322 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 40 Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Glu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 200 Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 215

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Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu
Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu
Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu
                               265
Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe
Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His
Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala
Gln Pro
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Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp
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Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser
Ile Leu Lys Asn Leu Glu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro
Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg
Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln
Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Ser Glu Gly Gly Gly
Ser Glu Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser
Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr
Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser
Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu
Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu
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Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro 230 235 Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 280 Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala 295 Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 268 <211> <212> PRT <213> Artificial Sequence <221> MUTAGEN <222> 1-307 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 40 Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu His Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln 135 Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp 150 Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 200 Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala

220 210 215 Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln 230 Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 305 <210> 269 <211> 322 <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-322 <223> <400> 269 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu His Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 135 Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly
165 170 175 Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 185

Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro

Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser

Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 230 235 Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His 295 Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 270 <211> 349 <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-349 <223> <400> 270 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 40 Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu His Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala Ser Glu Gly Gly Ger Glu Gly Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr 170 Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser 185 Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro

225	230	235	240
		Leu Ser Gln Leu His Se 250 25	_
Leu Phe Leu Tyr G	ln Gly Leu Leu Gln i 265	Ala Leu Glu Gly Ile Se 270	r Pro
Glu Leu Gly Pro Tl 275	hr Leu Asp Thr Leu (280	Gln Leu Asp Val Ala As 285	p Phe
Ala Thr Thr Ile To 290	rp Gln Gln Met Glu (295	Glu Leu Gly Met Ala Pr 300	o Ala
Leu Gln Pro Thr G	ln Gly Ala Met Pro A 310	Ala Phe Ala Ser Ala Ph 315	e Gln 320
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Gln Pro Pro Leu Pro 20	ro Leu Leu Asp Phe 1 25	Asn Asn Leu Asn Gly Gl 30	u Asp
Gln Asp Ile Leu Mo 35	et Glu Asn Asn Leu A 40	Arg Arg Pro Asn Leu Gl 45	u Ala
Phe Asn Arg Ala Va 50	al Lys Ser Leu Gln 1 55	Asn Ala Ser Ala Ile Gl 60	u Ser
Ile Leu Lys Asn Le 65	eu Phe Pro Cys Leu I 70	Pro Leu Ala Thr Ala Al 75	a Pro 80
Thr Arg His Pro I		Gly Asp Trp Asn Glu Ph 90 95	e Arg
Arg Lys Leu Thr Pl 100	he Tyr Leu Lys Thr I 105	Leu Glu Asn Ala Gln Al 110	a Gln
Gln Tyr Val Ile G			
	10 GIY Arg IIe Ser I 120	Pro Gly Gly Gly Ser Gl 125	y Gly
Gly Ser Asn Met Al	120		
130	120 la Thr Pro Leu Gly F 135	125 Pro Ala Ser Ser Leu Pr	o Gln
Ser Phe Leu Leu Ly 145 Gly Ala Ala Leu G	la Thr Pro Leu Gly I 135 ys Cys Leu Glu Gln V 150 In Glu Lys Leu Cys A	125 Pro Ala Ser Ser Leu Pr 140 Val Arg Lys Ile Gln Gl	y Asp 160
Ser Phe Leu Leu Ly 145 Gly Ala Ala Leu G	120 la Thr Pro Leu Gly H 135 ys Cys Leu Glu Gln V 150 ln Glu Lys Leu Cys A 65	Pro Ala Ser Ser Leu Pr 140 Val Arg Lys Ile Gln Gl 155 Ala Thr Tyr Lys Leu Cy	y Asp 160 s His
Ser Phe Leu Leu Ly 145 Gly Ala Ala Leu Gi 16 Pro Glu Glu Leu Va 180	la Thr Pro Leu Gly I 135 ys Cys Leu Glu Gln V 150 In Glu Lys Leu Cys A 65 al Leu Leu Gly His S 185	Pro Ala Ser Ser Leu Pr 140 Val Arg Lys Ile Gln Gl 155 Ala Thr Tyr Lys Leu Cy 170 Ser Leu Gly Ile Pro Tr	y Asp 160 s His 5

Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln 230 Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu 250 Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 295 Ala Gln Pro 305 <210> 272 <211> 322 <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-322 <223> <400> 272 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 1.0 Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Phe Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 120 Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly 165 170 Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 185 Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 215 Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu

225	230	235 240	0
Glu Gly Ile Ser Pro	Glu Leu Gly Pro Thr	Leu Asp Thr Leu Gln Leu	u
245	250	255	
Asp Val Ala Asp Phe	Ala Thr Thr Ile Trp	Gln Gln Met Glu Glu Let	u
260	265	270	
Gly Met Ala Pro Ala	Leu Gln Pro Thr Gln	Gly Ala Met Pro Ala Phe	9
275	280	285	
Ala Ser Ala Phe Gln	Arg Arg Ala Gly Gly	Val Leu Val Ala Ser His	5
290	295	300	
Leu Gln Ser Phe Leu	Glu Val Ser Tyr Arg	Val Leu Arg His Leu Ala	_
305	310	315 320	
Gln Pro			
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<400> 273			
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Gln Pro Pro Leu Pro	Leu Leu Asp Phe Asn	Asn Leu Asn Gly Glu Asp	Þ
20	25	30	
Gln Asp Ile Leu Met	Glu Asn Asn Leu Arg	Arg Pro Asn Leu Glu Ala	a
35	40	45	
Phe Asn Arg Ala Val	Lys Ser Leu Gln Asn	Ala Ser Ala Ile Glu Ser	r
50	55	60	
Ile Leu Lys Asn Leu	Phe Pro Cys Leu Pro	Leu Ala Thr Ala Ala Pro	>
65	70	75 80	
Thr Arg His Pro Ile	His Ile Lys Asp Gly	Asp Trp Asn Glu Phe Arc	3
85	90	95	
Arg Lys Leu Thr Phe	Tyr Leu Lys Thr Leu	Glu Asn Ala Gln Ala Glr	ב
100	105	110	
Gln Tyr Val Ile Glu	Gly Arg Ile Ser Pro	Gln Pro Pro Val Asn Ala	a
115	120	125	
Gly Gly Gly Ser Gly	Gly Gly Ser Gly Gly	Gly Ser Glu Gly Gly Gly	Y
130	135	140	
Ser Glu Gly Gly Gly	Ser Glu Gly Gly Gly	Ser Glu Gly Gly Gly Ser	
145	150	155 160	
Gly Gly Gly Ser Gly	Ser Gly Asp Phe Asp	Tyr Glu Asn Met Ala Thr	r
165	170	175	
Pro Leu Gly Pro Ala	Ser Ser Leu Pro Gln	Ser Phe Leu Leu Lys Ser	r
180	185	190	
Leu Glu Gln Val Arg	Lys Ile Gln Gly Asp	Gly Ala Ala Leu Gln Glu	ı
195	200	205	
Lys Leu Cys Ala Thr	Tyr Lys Leu Cys His	Pro Glu Glu Leu Val Leu	1
210	215	220	
Leu Gly His Ser Leu	Gly Ile Pro Trp Ala	Pro Leu Ser Ser Cys Pro	
225	230	235 240	

Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro 265 Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln $\hbox{Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu}\\$ Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 345 <210> 274 <211> <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-307 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 40 Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Ser Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 120 Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln 135 Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 185 Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 215

Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln 230 235 Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 295 Ala Gln Pro 305 <210> <211> 322 <212> PRT Artificial Sequence <220> MUTAGEN <221> <222> 1-322 <223> <400> 275 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Ser Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 200 Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 215 Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu

Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His 295 Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 276 <211> 349 <212> PRT Artificial Sequence <213> <220> MUTAGEN <221> <222> 1-349 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 10 Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Ser Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala Ser Glu Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser 185 Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro 230 235

Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly 250 Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro 265 Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 340 <210> 277 307 <211> <212> PRT<213> Artificial Sequence <220> MUTAGEN <221> <222> 1-307 <223> <400> 277 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Tyr Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His 170 Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 185 Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 215

Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln

225 230 235 Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu 245 250 Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 265 Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 305 <210> 278 <211> 322 <212> PRT Artificial Sequence <213> <220> MUTAGEN <221> <222> 1-322 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Tyr Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 120 Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 135 Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 185 Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu

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235

230

Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu 250 Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 279 <210> <211> 349 <212> <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-349 <223> <400> 279 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 10 Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Tyr Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala 120 Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser 185 Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly

245 250 255 Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro 265 Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 275 280 285Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 280 307 <211> <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-307 <223> <400> 280 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 25 Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg Arg Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 185 Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln

Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 295 Ala Gln Pro <210> 281 <211> 322 <212> PRT Artificial Sequence <220> MUTAGEN <221> <222> 1-322 <223> <400> 281 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg Arg Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser 150 155 Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Tle Gln Gly Asp Gly 165 170 175Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 200 Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 215 Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu

245 250 255 Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu 265 Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe 280 Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His 295 Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 282 <211> 349 <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN 1-349 <223> <400> 282 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg Arg Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala Ser Glu Gly Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu 215

Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro

Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly

Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 280 Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 345 <210> 283 <211> 307 <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-307 <223> <400> 283 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg Thr Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp 150 155 Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 200 Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 215 Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln

Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu 245 250 255

Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 260 265 270

Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser 275 280 285

His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 290 295 300

Ala Gln Pro

<210> 284

<211> 322

<212> PRT

<213> Artificial Sequence

<220> <221>

MUTAGEN

<222> 1-322

<223>

<400> 284

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 1 $$ 5 $$ 10 $$ 15

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 20 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 55 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg Thr Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln
100 105 110

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 115 120 125

Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 130 135 140

Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser 145 150 155 160

Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly 165 170 175

Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro

Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 195 200 205

Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 210 215 220

Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 225 230 235 240

Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu 245 250 255

Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu 265 Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 285 <211> 349 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-349 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg Thr Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala Gly Gly Gly Ser Gly Gly Gly Gly Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser 185 Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly

Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro 265 Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 280 Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 286 307 <211> <212> PRT <213> Artificial Sequence <220> MUTAGEN <221> <222> 1-307 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 10 Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 25 Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 40 Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg Asn Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 90 Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 120 Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 185 Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 200 Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu

> 245 250 255

Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 265

Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser 280

His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu

Ala Gln Pro 305

<210> 287

<211> 322 <212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN <222> 1-322

<223>

<400>

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 25

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro

Thr Arg Asn Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 120

Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 135

Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser

Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly 165

Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 185

Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 200

Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 215

Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu

Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu

Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe 280 Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 288 <211> 349 <212> <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-349 <223> <400> 288 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg Asn Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala 120 Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro 235 Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly

252/348

Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro

> 260 265 270

Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 280

Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala

Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln

Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu

Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro

<210> 289

<211> 307

<212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN

<222> 1-307

<223>

<400> 289

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro

Thr Arg Ser Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 115 120 125

Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln 135

Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp

Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His

Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala

Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu

Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala

Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln

Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu 250

Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 295 Ala Gln Pro <210> 290 <211> 322 <212> <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-322 <223> <400> 290 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 10 Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg Ser Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 120 Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 235 Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu 250 Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu

270 265

Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe 280

Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His

Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala

Gln Pro

<210>

349 <211> <212> PRT

<213> Artificial Sequence

260

<220>

MUTAGEN <221>

<222> 1-349

<223>

291 <400>

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro

Thr Arg Ser Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Ser Glu Gly Gly Gly

Ser Glu Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser 155

Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr

Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser

Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu 200

Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu

Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro

Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly

Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro 260 265

Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 280 Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 292 <211> 307 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-307 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 25 Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile Ile Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 185 Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu

Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 260 265 270

Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser 275 280 285

His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 290 295 300

Ala Gln Pro

<210> 293

<211> 322 <212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN

<222> 1-322

<223>

<400> 293

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 1 $$ 5 $$ 10 $$ 15

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 20 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile Ile Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 100 \$105\$

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 115 120 125

Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 130 135 140

Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser 145 150 150 155 160

Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly

Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro

Glu Glu Leu Val Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 195 200 205

Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 210 215 220

Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 225 230 230 240

Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu 245 250 255

Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu

260 265 270

Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe 275 280 285

Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His 290 295 300

Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala 305 310 315 320

Gln Pro

<210> 294

<211> 349 <212> PRT

<212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN

<222> 1-349

<223>

<400> 294

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 20 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 55 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile Ile Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 100 105 110

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala 115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Gly Gly Gly Gly Gly 130 135 140

Ser Glu Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser 145 150 155 160

Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr 165 $$ 170 $$ 175

Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser 180 185 190

Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu 195 200 205

Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu 210 215 220

Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro 225 230 235 240

Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly
245 250 255

Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro $260 \hspace{1.5cm} 265 \hspace{1.5cm} 270 \hspace{1.5cm}$

Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 280 Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 295 <211> 307 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-307 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 25 Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile Leu Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln 135 Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 185 Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 200 Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu

Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 260 265 270

Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser 275 280 285

His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 290 295 300

Ala Gln Pro

<210> 296

<211> 322 <212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN

<222> 1-322

<223>

<400> 296

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 1 5 10 15

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 20 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 55 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile Leu Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 100 105 110

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 115 120 125

Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 130 135 140

Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser 145 150 155 160

Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly 165 170 175

Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 180 185 190

Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 195 200 205

Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 210 225 220

Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 225 230 235 240

Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu 245 250 255

Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu 260 265 270

Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe 280 Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 297 349 <211> <212> PRT Artificial Sequence <220> MUTAGEN <221> <222> 1-349 <223> <400> 297 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile Leu Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val As
n Ala 115 120 125 Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Gly Gly Gly Gly Ser Glu Gly Gly Ger Glu Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu 215 Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro 265

Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 280 Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala 295 Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln 310 315 Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 298 <211> 307 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-307 <223> <400> 298 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys . 10 Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 25 Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile Ala Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 120 Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln 135 Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala

225 230 235 240

Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu 245 250 255

Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu

Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala

Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln

Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala

260 265 270

Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser 275 280 285

His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 290 295 300

Ala Gln Pro 305

<210> 299

<211> 322 <212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN

<222> 1-322

<223>

<400> 299

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 1 5 10 15

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 20 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile Ala Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 100 105 110

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro $115 \hspace{1cm} 120 \hspace{1cm} 125$

Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 130 135 140

Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser 145 150 155 160

Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly
165 170 175

Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 180 185 190

Glu Glu Leu Val Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 195 200 205

Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 210 215 220

Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 225 230 240

Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu
245 250 255

Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu 260 265 270

Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 300 <211> 349 <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-349 <223> <400> 300 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 40 Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile Ala Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Glu Gly Gly Gly 135 Ser Glu Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro

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Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe

275 280 285

Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala 290 295 300

Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln 305 310 315 320

Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu 325 330 335

Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 340 345

<210> 301

<211> 307

<212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN

<222> 1-307

<223>

<400> 301

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 1 5 10 15

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 20 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 55 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile Gln Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 100 105 110

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 115 120 125

Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln 130 135 140

Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp 145 150 155 160

Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His
165 170 175

Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 180 185 190

Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 195 200 205

Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 210 215 220

Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln 225 230 235 240

Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu 245 250 255

Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 260 265 270

Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser 275 280 285

His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 290 295 300

Ala Gln Pro 305

<210> 302 <211> 322

<212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN <222> 1-322

<222>

<400> 302

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 1 5 10 15

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 20 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 55 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile Gln Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln
100 105 110

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro $115 \\ 120 \\ 125$

Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 130 135 140

Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser 145 150 155 160

Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly
165 170 175

Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 180 185 190

Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 195 200 205

Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 210 215 220

Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 225 230 235 240

Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu 245 250 255

Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu 260 265 270

Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe

275 280 285

Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His 290 295 300

Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala 305 310 . 315 320

Gln Pro

<210> 303

<211> 349 <212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN

<222> 1-349

<223>

<400> 303

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 1 $$ 10 $$ 15

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 20 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 55 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile Gln Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 100 105 110

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala 115 120 125

Ser Glu Gly Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser 145 150 155 160

Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr $165 \\ \hspace{1.5cm} 170 \\ \hspace{1.5cm} 175$

Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Lys Ser 180 185 190

Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu
195 200 205

Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu 210 215 220

Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro 225 230 235 240

Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly 245 250 255

Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro 260 265 270

Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 275 280 285

Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala 295 Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 304 <211> 307 <212> PRT <213> Artificial Sequence <220> MUTAGEN <221> <222> 1-307 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 25 Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile Met Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 120 Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 185 Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 200 Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 265

Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser 275 280 285

His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 290 295 300

Ala Gln Pro 305

<210> 305

<211> 322 <212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN

<222> 1-322

<223>

<400> 305

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 20 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 55 60°

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile Met Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 100 105 110

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 115 120 125

Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 130 135 140

Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser 145 150 155 160

Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly 165 170 175

Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 180 185 190

Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 195 200 205

Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 210 215 220

Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 225 230 235 240

Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu 245 250 255

Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu 260 265 270

Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe 275 280 285

Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His 295 Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala 310 315 Gln Pro <210> 306 <211> <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-349 <223> <400> 306 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile Met Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala Ser Glu Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe

Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala 290 295 300

Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln 305 310 315 320

Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu 325 330 335

Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 340 345

<210> 307 <211> 307

<212> PRT <213> Artificial Sequence

<220>

<221> MUTAGEN <222> 1-307

<223>

<400> 307

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 1 5 10 15

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 20 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 55 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile Ser Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 100 105 110

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly
115 120 125

Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln
130 135 140

Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp 145 150 155 160

Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His 165 170 175

Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 180 185 190

Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu

Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 210 215 220

Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln 225 230 235 240

Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu 245 250 255

Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 260 265 270

Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser

275 280 285

His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 290 295 300

Ala Gln Pro

<210> 308 <211> 322

<212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN

<222> 1-322

<223>

<400> 308

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 1 5 10 15

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 20 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 55 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile Ser Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 100 105 110

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 115 120 125

Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 130 135 140

Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser 145 150 155 160

Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly 165 170 175

Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 180 185 190

Glu Glu Leu Val Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 195 200 205

Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 210 215 220

Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 225 230 235 240

Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu
245 250 255

Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu 260 265 270

Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe 275 280 285

Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His 290 295 300

Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala 305 310 315 320

Gln Pro

<210> 309 <211> 349

<212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN

<222> 1-349

<223>

<400> 309

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 55 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile Ser Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 100 105 110

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala 115 120 125

Ser Glu Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser 145 Ser Glu Gly Gly Ser 150 Ser 155 Ser 160

Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr 165 170 175

Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser 180 185 190

Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu 195 200 205

Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu 210 215 220

Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro 225 230 235 240

Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly 245 250 255

Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro 260 265 270

Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 275 280 285

Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala

300

Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln

Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu

Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro

295

<210> 310 <211> 307

290

<212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN

<222> 1-307

<223>

<400> 310

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 1 5 10 15

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 20 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile Tyr Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 100 105 110

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly
115 120 125

Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln 130 135 140

Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp 145 150 150 155 160

Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His $165 \hspace{1.5cm} 170 \hspace{1.5cm} 175$

Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 180 185 190

Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu
195 200 205

Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 210 215 220

Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln 225 230 235 240

Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu 245 250 255

Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 260 265 270

Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser 275 280 285

His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 290 295 300

Ala Gln Pro 305

<210> 311

<211> 322 <212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN

<222> 1-322

<223>

<400> 311

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 1 5 10 15

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 20 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 55 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile Tyr Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln 100 105 110

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 115 120 125

Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 130 135 140

Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser 145 150 155 160

Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly

Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro

Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 195 200 205

Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 210 215 220

Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 225 230 235 240

Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu 245 250 255

Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu 260 265 270

Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe 275 280 285

Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His

290 295 300 Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala 310 315 Gln Pro <210> 312 <211> 349 <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-349 <223> <400> 312 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile Tyr Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg $\hbox{Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln}$ Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gl
n Val Arg Lys Ile Gl
n Gly Asp Gly Ala Ala Leu Gl
n Glu 200 Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe

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Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala

295

Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 313 <211> 307 <212> PRT <213> Artificial Sequence <220> MUTAGEN <221> <222> 1-307 <400> 313 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile Val Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 115 120 125 Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu 250 Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser

His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 290 295 300

Ala Gln Pro 305

<210> 314

<211> 322 <212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN

<222> 1-322

<223>

<400> 314

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 1 5 10 15

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 20 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 55 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile Val Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 100 105 110

Glm Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro
115 120 125

Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 130 135 140

Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser 145 150 155 160

Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly
165 170 175

Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 180 185 190

Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 195 200 205

Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 210 215 220

Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 225 230 235 240

Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu 245 250 255

Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu 260 265 270

Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe 275 280 285

Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His $290 \hspace{1.5cm} 295 \hspace{1.5cm} 300 \hspace{1.5cm}$

Leu Gln 305	Ser	Phe	Leu	Glu 310	Val	Ser	Tyr	Arg	Val 315	Leu	Arg	His	Leu	Ala 320
Gln Pro														
<210> <211> <212> <213>	31! 34! PR'	9 F	cial	Sequence										
<220> <221> <222> <223>		ragei 349	4											
<400> 315														
Met Ala 1	Asn	Cys	Ser 5	Asn	Met	Ile	Asp	Glu 10	Ile	Ile	Thr	His	Leu 15	Lys
Gln Pro	Pro	Leu 20	Pro	Leu	Leu	Asp	Phe 25	Asn	Asn	Leu	Asn	Gly 30	Glu	Asp
Gln Asp	Ile 35	Leu	Met	Glu	Asn	Asn 40	Leu	Arg	Arg	Pro	Asn 45	Leu	Glu	Ala
Phe Asn 50	Arg	Ala	Val	Lys	Ser 55	Leu	Gln	Asn	Ala	Ser 60	Ala	Ile	Glu	Ser
Ile Leu 65	Lys	Asn	Leu	Leu 70	Pro	Cys	Leu	Pro	Leu 75	Ala	Thr	Ala	Ala	Pro 80
Thr Arg	His	Pro	Ile 85	Val	Ile	Lys	Asp	Gly 90	Asp	Trp	Asn	Glu	Phe 95	Arg
Arg Lys	Leu	Thr 100	Phe	Tyr	Leu	Lys	Thr 105	Leu	Glu	Asn	Ala	Gln 110	Ala	Gln
Gln Tyr	Val 115	Ile	Glu	Gly	Arg	Ile 120	Ser	Pro	Gln	Pro	Pro 125	Val	Asn	Ala
Gly Gly 130	Gly	Ser	Gly	Gly	Gly 135	Ser	Gly	Gly	Gly	Ser 140	Glu	Gly	Gly	Gly
Ser Glu 145	Gly	Gly	Gly	Ser 150		Gly	Gly	Gly	Ser 155	Glu	Gly	Gly	Gly	Ser 160
Gly Gly	Gly	Ser	Gly 165	Ser	Gly	Asp	Phe	Asp 170	Tyr	Glu	Asn	Met	Ala 175	Thr
Pro Leu	Gly	Pro 180	Ala	Ser	Ser	Leu	Pro 185	Gln	Ser	Phe	Leu	Leu 190	Lys	Ser
Leu Glu	Gln 195	Val	Arg	Lys	Ile	Gln 200	Gly	Asp	Gly	Ala	Ala 205	Leu	Gln	Glu
Lys Leu 210	Cys	Ala	Thr	Tyr	Lys 215	Leu	Cys	His	Pro	Glu 220	Glu	Leu	Val	Leu
Leu Gly 225	His	Ser	Leu	Gly 230	Ile	Pro	Trp	Ala	Pro 235	Leu	Ser	Ser	Cys	Pro 240
Ser Gln	Ala	Leu	G1n 245	Leu	Ala	Gly	Cys	Leu 250	Ser	Gln	Leu	His	Ser 255	Gly
Leu Phe	Leu	туr 260	Gln	Gly	Leu	Leu	Gln 265	Ala	Leu	Glu	Gly	Ile 270	Ser	Pro
Glu Leu	Gly 275	Pro	Thr	Leu	Asp	Thr 280	Leu	Gln	Leu	Asp	Val 285	Ala	Asp	Phe
Ala Thr 290	Thr	Ile	Trp	Gln	Gln 295	Met	Glu	Glu	Leu	Gly 300	Met	Ala	Pro	Ala

Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 316 <211> 307 <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-307 <223> <400> 316 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Arg Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln 135 Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His 170 Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 215 Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser

His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu

290 295 300

Ala Gln Pro 305

<210> 317 <211> 322

<211> 322 <212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN

<222> 1-322

<223>

<400> 31

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 1 5 10 15

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 20 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 55 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile His Ile Arg Asp Gly Asp Trp Asn Glu Phe Arg $85 \hspace{1.5cm} 90 \hspace{1.5cm} \cdot \hspace{1.5cm} 95$

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 100 105 110

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro $115 \\ 120 \\ 125$

Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 130 135 140

Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser 145 150 150 160

Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly 165 170 175

Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 180 185 190

Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 195 200 205

Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 210 215 220

Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 225 230 235 240

Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu 245 250 255

Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu 260 265 270

Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe

Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His 290 295 300

Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 318 <211> 349 <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-349 <223> <400> 318 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 25 Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Arg Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala 120 . Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu 215 Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro 235 Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 280 Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala

Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln

305 310 315 320 Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu 330 Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 319 <210> 307 <211> <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-307 <223> <400> 319 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 10 Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Glu Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 120 Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 215 Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln 235 Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser 280 His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu

Ala Gln Pro 305

<210> 320 <211> 322

<212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN <222> 1-322

<223>

<400> 320

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 1 $$ 5 $$ 10 $$ 15

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 20 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 55 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile His Ile Glu Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 100 105 110

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 115 120 125

Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 130 135 140

Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser 145 150 155 160

Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly
165 170 175

Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 180 185 190

Glu Glu Leu Val Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 195 200 205

Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 210 215 220

Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 225 230 230 235

Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu 245 250 255

Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu 260 265 270

Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe

Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His

Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala

305 310 315 320 Gln Pro <210> 321 <211> <212> PRT Artificial Sequence <213> <220> MUTAGEN <221> <222> 1-349 <223> <400> 321 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Glu Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 . Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu 200 Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln

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Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu 330 Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 322 <211> 307 <212> PRT Artificial Sequence <213> <220> MUTAGEN <222> 1-307 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 40 Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Pro Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln 135 Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 185 Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu 250 Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala

Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser

His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu

Ala Gln Pro 305

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315

310

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Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln

Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 325 307 <211> <212> PRT Artificial Sequence <213> <220> <221> MUTAGEN <222> 1-307 <223> <400> 325 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys His Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His 170 Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 185 Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser 280 His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 295

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Ala Gln Pro

305

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Gln Asp	Ile Leu 35	Met	Glu	Asn	Asn 40	Leu	Arg	Arg	Pro	Asn 45	Leu	Glu	Ala
Phe Asn 50	Arg Ala	Val	Lys	Ser 55	Leu	Gln	Asn	Ala	Ser 60	Ala	Ile	Glu	Ser
Ile Leu 65	Lys Asn		Leu 70	Pro	Cys	Leu	Pro	Leu 75	Ala	Thr	Ala	Ala	Pro 80
Thr Arg	His Pro	Ile 85	His	Ile	Lys	His	Gly 90	Asp	Trp	Asn	Glu	Phe 95	Arg
Arg Lys	Leu Thr 100	Phe	Tyr	Leu	Lys	Thr 105	Leu	Glu	Asn	Ala	Gln 110	Ala	Gln
Gln Tyr	Val Ile 115	Glu	Gly	Arg	Ile 120	Ser	Pro	Gly	Glu	Pro 125	Ser	Gly	Pro
Ile Ser 130	Thr Ile	Asn	Pro	Ser 135	Pro	Pro	Ser	Lys	Glu 140	Ser	His	Lys	Ser
Pro Asn 145	Met Ala		Pro 150	Leu	Gly	Pro	Ala	Ser 155	Ser	Leu	Pro	Gln	Ser 160
Phe Leu	Leu Lys	Cys 165	Leu	Glu	Gln	Val	Arg 170	Lys	Ile	Gln	Gly	Asp 175	Gly
Ala Ala	Leu Gln 180	G1u	Lys	Leu	Cys	Ala 185	Thr	Tyr	Lys	Leu	Cys 190	His	Pro
Glu Glu	Leu Val 195	Leu	Leu	Gly	His 200	Ser	Leu	Gly	Ile	Pro 205	Trp	Ala	Pro
Leu Ser 210	Ser Cys	Pro	Ser	Gln 215	Ala	Leu	Gln	Leu	Ala 220	Gly	Cys	Leu	Ser
Gln Leu 225	His Ser		Leu 230	Phe	Leu	Tyr	Gln	Gly 235	Leu	Leu	Gln	Ala	Leu 240
Glu Gly	Ile Ser	Pro 245	Glu	Leu	Gly	Pro	Thr 250	Leu	Asp	Thr	Leu	Gln 255	Leu
Asp Val	Ala Asp 260	Phe .	Ala	Thr	Thr	Ile 265	Trp	Gln	Gln	Met	Glu 270	Glu	Leu
Gly Met	Ala Pro 275	Ala	Leu	Gln	Pro 280	Thr	Gln	Gly	Ala	Met 285	Pro	Ala	Phe
Ala Ser . 290	Ala Phe	Gln .	Arg	Arg 295	Ala	Gly	Gly	Val	Leu 300	Val	Ala	Ser	His
Leu Gln 305	Ser Phe		Glu 310	Val	Ser	Tyr	Arg	Val 315	Leu	Arg	His	Leu	Ala 320

Gln Pro

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325 330 335

Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 340 345

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<222> 1-307

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Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 55 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile His Ile Lys Asn Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 100 \$105\$

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 115 120 125

Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln 130 135 140

Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp 145 150 155 160

Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His 165 170 175

Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 180 185 190

Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 195 200 205

Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 210 215 220

Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln 225 230 235 240

Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu 245 250 255

Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 260 265 270

Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser 275 280 285

His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 290 295 300

Ala Gln Pro

305

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Gln	Asp	Ile 35	Leu	Met	Glu	Asn	Asn 40	Leu	Arg	Arg	Pro	Asn 45	Leu	Glu	Ala
Phe	Asn 50	Arg	Ala	Val	Lys	Ser 55	Leu	Gln	Asn	Ala	Ser 60	Ala	Ile	Glu	Ser
Ile 65	Leu	Lys	Asn	Leu	Leu 70	Pro	Cys	Leu	Pro	Leu 75	Ala	Thr	Ala	Ala	Pro 80
Thr	Arg	His	Pro	Ile 85	His	Ile	Lys	Asn	Gly 90	Asp	Trp	Asn	Glu	Phe 95	Arg
Arg	Lys	Leu	Thr 100	Phe	Tyr	Leu	Lys	Thr 105	Leu	Glu	Asn	Ala	Gln 110	Ala	Gln
Gln	Tyr	Val 115	Ile	Glu	Gly	Arg	Ile 120	Ser	Pro	Gly	Glu	Pro 125	Ser	Gly	Pro
Ile	Ser 130	Thr	Ile	Asn	Pro	Ser 135	Pro	Pro	Ser	Lys	Glu 140	Ser	His	Lys	Ser
Pro 145	Asn	Met	Ala	Thr	Pro 150	Leu	Gly	Pro	Ala	Ser 155	Ser	Leu	Pro	Gln	Ser 160
Phe	Leu	Leu	Lys	Cys 165	Leu	Glu	Gln	Val	Arg 170	Lys	Ile	Gln	Gly	Asp 175	Gly
Ala	Ala	Leu	Gln 180	Glu	Lys	Leu	Cys	Ala 185	Thr	Tyr	Lys	Leu	Cys 190	His	Pro
Glu	Glu	Leu 195	Val	Leu	Leu	Gly	His 200	Ser	Leu	Gly	Ile	Pro 205	Trp	Ala	Pro
Leu	Ser 210	Ser	Cys	Pro	Ser	Gln 215	Ala	Leu	Gln	Leu	Ala 220	Gly	Cys	Leu	Ser
Gln 225	Leu	His	Ser	Gly	Leu 230	Phe	Leu	Tyr	Gln	Gly 235	Leu	Leu	Gln	Ala	Leu 240
Glu	Gly	Ile	Ser	Pro 245	Glu	Leu	Gly	Pro	Thr 250	Leu	Asp	Thr	Leu	Gln 255	Leu
Asp	Val	Ala	Asp 260	Phe	Ala	Thr	Thr	Ile 265	Trp	Gln	Gln	Met	Glu 270	Glu	Leu
Gly	Met	Ala 275	Pro	Ala	Leu	Gln	Pro 280	Thr	Gln	Gly	Ala	Met 285	Pro	Ala	Phe
Ala	Ser 290	Ala	Phe	Gln	Arg	Arg 295	Ala	Gly	Gly	Val	Leu 300	Val	Ala	Ser	His
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Gln Asp	Ile Le 35	u Met	Glu	Asn	Asn 40	Leu	Arg	Arg	Pro	Asn 45	Leu	Glu	Ala
Phe Asn 50	Arg Al	a Val	Lys	Ser 55	Leu	Gln	Asn	Ala	Ser 60	Ala	Ile	Glu	Ser
Ile Leu 65	Lys As	n Leu	Leu 70	Pro	Cys	Leu	Pro	Leu 75	Ala	Thr	Ala	Ala	Pro 80
Thr Arg	His Pr	o Ile 85	His	Ile	Lys	Asn	Gly 90	Asp	Trp	Asn	Glu	Phe 95	Arg
Arg Lys	Leu Th		Tyr	Leu	Lys	Thr 105	Leu	Glu	Asn	Ala	Gln 110	Ala	Gln
Gln Tyr	Val II 115	e Glu	Gly	Arg	Ile 120	Ser	Pro	Gln	Pro	Pro 125	Val	Asn	Ala
Gly Gly 130	Gly Se	r Gly	Gly	Gly 135	Ser	Gly	Gly	Gly	Ser 140	Glu	Gly	Gly	Gly
Ser Glu 145	Gly Gl	y Gly	Ser 150	Glu	Gly	Gly	Gly	Ser 155	Glu	Gly	Gly	Gly	Ser 160
Gly Gly	Gly Se	r Gly 165	Ser	Gly	Asp	Phe	Asp 170	Tyr	Glu	Asn	Met	Ala 175	Thr
Pro Leu	Gly Pr 18		Ser	Ser	Leu	Pro 185	Gln	Ser	Phe	Leu	Leu 190	Lys	Ser
Leu Glu	Gln Va 195	l Arg	Lys	Ile	Gln 200	Gly	Asp	Gly	Ala	Ala 205	Leu	Gln	Glu
Lys Leu 210	Cys Al	a Thr	Tyr	Lys 215	Leu	Cys	His	Pro	Glu 220	Glu	Leu	Val	Leu
Leu Gly 225	His Se	r Leu	Gly 230	Ile	Pro	Trp	Ala	Pro 235	Leu	Ser	Ser	Cys	Pro 240
Ser Gln	Ala Le	u Gln 245	Leu	Ala	Gly	Cys	Leu 250	Ser	Gln	Leu	His	Ser 255	Gly
Leu Phe	Leu Ty 26		Gly	Leu	Leu	Gln 265	Ala	Leu	Glu	Gly	Ile 270	Ser	Pro
Glu Leu	Gly Pr 275	o Thr	Leu	Asp	Thr 280	Leu	Gln	Leu	Asp	Val 285	Ala	Asp	Phe
Ala Thr 290	Thr Il	e Trp	Gln	Gln 295	Met	Glu	Glu	Leu	Gly 300	Met	Ala	Pro	Ala
Leu Gln 305	Pro Th	r Gln	Gly 310	Ala	Met	Pro	Ala	Phe 315	Ala	Ser	Ala	Phe	Gln 320
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Gln Asp	Ile Leu M 35	et Glu Asn	Asn Leu 40	Arg Arg	Pro As		Glu	Ala
Phe Asn 50	Arg Ala V	al Lys Ser 55	Leu Gln	Asn Ala	Ser Al	a Ile	Glu	Ser
Ile Leu 65	Lys Asn L	eu Leu Pro 70	Cys Leu	Pro Leu 75	Ala Ti	ır Ala		<i>Pro</i> 80
Thr Arg	His Pro I	le His Ile 5	Lys Ile	Gly Asp 90	Trp As	n Glu	Phe 95	Arg
Arg Lys	Leu Thr P	he Tyr Leu	Lys Thr 105	Leu Glu	Asn Al	a Gln 110	Ala	Gln
Gln Tyr	Val Ile G 115	lu Gly Arg	Ile Ser 120	Pro Gly	Glu Pi 12		Gly	Pro
Ile Ser 130	Thr Ile A	sn Pro Ser 135		Ser Lys	Glu Se 140	er His	Lys	Ser
Pro Asn 145	Met Ala T	hr Pro Leu 150	Gly Pro	Ala Ser 155	Ser Le	eu Pro		Ser 160
Phe Leu		ys Leu Glu 65	. Gln Val	Arg Lys 170	Ile G	n Gly	Asp 175	Gly
Ala Ala	Leu Gln G 180	lu Lys Leu	Cys Ala 185	Thr Tyr	Lys Le	eu Cys 190	His	Pro
Glu Glu	Leu Val L 195	eu Leu Gly	His Ser 200	Leu Gly	Ile Pi 20		Ala	Pro
Leu Ser 210	Ser Cys P	ro Ser Gln 215		Gln Leu	Ala G1 220	.у Суз	Leu	Ser
Gln Leu 225	His Ser G	ly Leu Phe 230	Leu Tyr	Gln Gly 235		a Gln		Leu 240
Glu Gly		ro Glu Leu 45	Gly Pro	Thr Leu 250	Asp Th	ır Leu	Gln 255	Leu
Asp Val	Ala Asp P 260	he Ala Thr	Thr Ile 265		Gln Me	et Glu 270	Glu	Leu
Gly Met	Ala Pro A 275	la Leu Gln	Pro Thr 280	Gln Gly	Ala Me		Ala	Phe
Ala Ser 290	Ala Phe G	ln Arg Arg 295		Gly Val	Leu Va	ıl Ala	Ser	His
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Gln Pro								

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Gln Asp	Ile Leu 35	ı Met G	lu Asn	Asn 40	Leu	Arg	Arg	Pro	Asn 45	Leu	Glu	Ala
Phe Asn 50	Arg Ala	Val L	ys Ser 55	Leu	Gln	Asn	Ala	Ser 60	Ala	Ile	Glu	Ser
Ile Leu 65	Lys Asr	Leu L 7		Cys	Leu	Pro	Leu 75	Ala	Thr	Ala	Ala	Pro 80
Thr Arg	His Pro	Ile H 85	is Ile	Lys	Ile	Gly 90	Asp	Trp	Asn	Glu	Phe 95	Arg
Arg Lys	Leu Thr		yr Leu	Lys	Thr 105	Leu	Glu	Asn	Ala	Gln 110	Ala	Gln
Gln Tyr	Val I1e 115	Glu G	ly Arg	Ile 120	Ser	Pro	Gln	Pro	Pro 125	Val	Asn	Ala
Gly Gly 130	Gly Ser	Gly G	ly Gly 135		Gly	Gly	Gly	Ser 140	Glu	Gly	Gly	Gly
Ser Glu 145	Gly Gly		er Glu 50	Gly	Gly	Gly	Ser 155	Glu	Gly	Gly	Gly	Ser 160
Gly Gly	Gly Ser	Gly S 165	er Gly	Asp	Phe	Asp 170	Tyr	Glu	Asn	Met	Ala 175	Thr
Pro Leu	Gly Pro		er Ser	Leu	Pro 185	Gln	Ser	Phe	Leu	Leu 190	Lys	Ser
Leu Glu	Gln Val 195	Arg L	ys Ile	Gln 200	Gly	Asp	Gly	Ala	Ala 205	Leu	Gln	Glu
Lys Leu 210	Cys Ala	Thr T	yr Lys 215		Cys	His	Pro	Glu 220	Glu	Leu	Val	Leu
Leu Gly 225	His Ser		ly Ile 30	Pro	Trp	Ala	Pro 235	Leu	Ser	Ser	Cys	Pro 240
Ser Gln	Ala Leu	Gln L 245	eu Ala	Gly	Cys	Leu 250	Ser	Gln	Leu	His	Ser 255	Gly
Leu Phe	Leu Tyr 260		ly Leu	Leu	Gln 265	Ala	Leu	Glu	Gly	Ile 270	Ser	Pro
Glu Leu	Gly Pro 275	Thr L	eu Asp	Thr 280	Leu	Gln	Leu	Asp	Val 285	Ala	Asp	Phe
Ala Thr 290	Thr Ile	Trp G	ln Gln 295		Glu	Glu	Leu	Gly 300	Met	Ala	Pro	Ala
Leu Gln 305	Pro Thr		ly Ala 10	Met	Pro	Ala	Phe 315	Ala	Ser	Ala	Phe	Gln 320
Arg Arg	Ala Gly	Gly Va 325	al Leu	Val	Ala	Ser 330	His	Leu	Gln	Ser	Phe 335	Leu

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His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu

Ala Gln Pro 305

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Gln	Asp	Ile 35	Leu	Met	Glu	Asn	Asn 40	Leu	Arg	Arg	Pro	Asn 45	Leu	Glu	Ala
Phe	Asn 50	Arg	Ala	Val	Lys	Ser 55	Leu	Gln	Asn	Ala	Ser 60	Ala	Ile	Glu	Ser
Ile 65	Leu	Lys	Asn	Leu	Leu 70	Pro	Cys	Leu	Pro	Leu 75	Ala	Thr	Ala	Ala	Pro 80
Thr	Arg	His	Pro	Ile 85	His	Ile	Lys	Leu	Gly 90	Asp	Trp	Asn	Glu	Phe 95	Arg
Arg	Lys	Leu	Thr 100	Phe	Tyr	Leu	Lys	Thr 105	Leu	Glu	Asn	Ala	Gln 110	Ala	Gln
Gln	Tyr	Val 115	Ile	Glu	Gly	Arg	Ile 120	Ser	Pro	Gly	Glu	Pro 125	Ser	Gly	Pro
Ile	Ser 130	Thr	Ile	Asn	Pro	Ser 135	Pro	Pro	Ser	Lys	Glu 140	Ser	His	Lys	Ser
Pro 145	Asn	Met	Ala	Thr	Pro 150	Leu	Gly	Pro	Ala	Ser 155	Ser	Leu	Pro	Gln	Ser 160
Phe	Leu	Leu	Lys	Cys 165	Leu	Glu	Gln	Val	Arg 170	Lys	Ile	Gln	Gly	Asp 175	Gly
Ala	Ala	Leu	Gln 180	Glu	Lys	Leu	Cys	Ala 185	Thr	Tyr	Lys	Leu	Cys 190	His	Pro
Glu	Glu	Leu 195	Val	Leu	Leu	Gly	His 200	Ser	Leu	Gly	Ile	Pro 205	Trp	Ala	Pro
Leu	Ser 210	Ser	Cys	Pro	Ser	Gln 215	Ala	Leu	Gln	Leu	Ala 220	Gly	Cys	Leu	Ser
Gln 225	Leu	His	Ser	Gly	Leu 230	Phe	Leu	Tyr	Gln	Gly 235	Leu	Leu	Gln	Ala	Leu 240
Glu	Gly	Ile	Ser	Pro 245	Glu	Leu	Gly	Pro	Thr 250	Leu	Asp	Thr	Leu	Gln 255	Leu
Asp	Val	Ala	Asp 260	Phe	Ala	Thr	Thr	Ile 265	Trp	Gln	Gln	Met	Glu 270	Glu	Leu
Gly	Met	Ala 275	Pro	Ala	Leu	Gln	Pro 280	Thr	Gln	Gly	Ala	Met 285	Pro	Ala	Phe
Ala	Ser 290	Ala	Phe	Gln	Arg	Arg 295	Ala	Gly	Gly	Val	Leu 300	Val	Ala	Ser	His
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Gln	Pro														

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	Gln	Asp	Ile 35	Leu	Met	Glu	Asn	Asn 40	Leu	Arg	Arg	Pro	Asn 45	Leu	Glu	Ala
	Phe	Asn 50	Arg	Ala	Val	Lys	Ser 55	Leu	Gln	Asn	Ala	Ser 60	Ala	Ile	Glu	Ser
	Ile 65	Leu	Lys	Asn	Leu	Leu 70	Pro	Cys	Leu	Pro	Leu 75	Ala	Thr	Ala	Ala	Pro 80
	Thr	Arg	His	Pro	Ile 85	His	Ile	Lys	Leu	Gly 90	Asp	Trp	Asn	Glu	Phe 95	Arg
	Arg	Lys	Leu	Thr 100	Phe	Tyr	Leu	Lys	Thr 105	Leu	Glu	Asn	Ala	Gln 110	Àla	Gln
	Gln	Tyr	Val 115	Ile	Glu	Gly	Arg	Ile 120	Ser	Pro	Gln	Pro	Pro 125	Val	Asn	Ala
	Gly	Gly 130	Gly	Ser	Gly	Gly	Gly 135	Ser	Gly	Gly	Gly	Ser 140	Glu	Gly	Gly	Gly
	Ser 145	Glu	Gly	Gly	Gly	Ser 150	Glu	Gly	Gly	Gly	Ser 155	Glu	Gly	Gly	Gly	Ser 160
	G1y	Gly	Gly	Ser	Gly 165	Ser	Gly	Asp	Phe	Asp 170	Tyr	Glu	Asn	Met	Ala 175	Thr
	Pro	Leu	Gly	Pro 180	Ala	Ser	Ser	Leu	Pro 185	Gln	Ser	Phe	Leu	Leu 190	Lys	Ser
	Leu	Glu	Gln 195	Val	Arg	Lys	Ile	Gln 200	Gly	Asp	Gly	Ala	Ala 205	Leu	Gln	Glu
	Lys	Leu 210	Cys	Ala	Thr	Tyr	Lys 215	Leu	Cys	His	Pro	Glu 220	Glu	Leu	Val	Leu
	Leu 225	Gly	His	Ser	Leu	Gly 230	Ile	Pro	Trp	Ala	Pro 235	Leu	Ser	Ser	Cys	Pro 240
	Ser	Gln	Ala	Leu	Gln 245	Leu	Ala	Gly	Cys	Leu 250	Ser	Gln	Leu	His	Ser 255	Gly
	Leu	Phe	Leu	Туr 260	Gln	Gly	Leu	Leu	G1n 265	Ala	Leu	Glu	Gly	Ile 270	Ser	Pro
	Glu	Leu	Gly 275	Pro	Thr	Leu	Asp	Thr 280	Leu	Gln	Leu	Asp	Val 285	Ala	Asp	Phe
	Ala	Thr 290	Thr	Ile	Trp	Gln	Gln 295	Met	Glu	Glu	Leu	Gly 300	Met	Ala	Pro	Ala
	Leu 305	Gln	Pro	Thr	Gln	Gly 310	Ala	Met	Pro	Ala	Phe 315	Ala	Ser	Ala	Phe	Gln 320
	Arg	Arg	Ala	Gly	Gly 325	Val	Leu	Val	Ala	Ser 330	His	Leu	Gln	Ser	Phe 335	Leu
	Glu	Val	Ser	Tyr	Arg	Val	Leu	Arg	His	Leu	Ala	Gln	Pro			

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<210> 339

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Gln	Pro	Pro	Leu 20	Pro	Leu	Leu	Asp	Phe 25	Asn	Asn	Leu	Asn	Gly 30	Glu	Asp
Gln	Asp	Ile 35	Leu	Met	Glu	Asn	Asn 40	Leu	Arg	Arg	Pro	Asn 45	Leu	Glu	Ala
Phe	Asn 50	Arg	Ala	Val	Lys	Ser 55	Leu	Gln	Asn	Ala	Ser 60	Ala	Ile	Glu	Ser
11e 65	Leu	Lys	Asn	Leu	Leu 70	Pro	Cys	Leu	Pro	Le u 75	Ala	Thr	Ala	Ala	Pro 80
Thr	Arg	His	Pro	Ile 85	His	Ile	Lys	Asp	Gly 90	Asp	Trp	Pro	Glu	Phe 95	Arg
Arg	Lys	Leu	Thr 100	Phe	Тух	Leu	Lys	Thr 105	Leu	Glu	Asn	Ala	Gln 110	Ala	Gln
Gln	Tyr	Val 115	Ile	Glu	Gly	Arg	Ile 120	Ser	Pro	Gln	Pro	Pro 125	Val	Asn	Ala
Gly	Gly 130	Gly	Ser	Gly	Gly	Gly 135	Ser	Gly	Gly	Gly	Ser 140	Glu	Gly	Gly	Gly
Ser 145	Glu	Gly	Gly	Gly	Ser 150	Glu	Gly	Gly	Gly	Ser 155	Glu	Gly	Gly	Gly	Ser 160
Gly	Gly	Gly	Ser	Gly 165	Ser	Gly	Asp	Phe	Asp 170	Tyr	Glu	Asn	Met	Ala 175	Thr
Pro	Leu	Gly	Pro 180	Ala	Ser	Ser	Leu	Pro 185	Gln	Ser	Phe	Leu	Leu 190	Lys	Ser
Leu	Glu	Gln 195	Val	Arg	Lys	Ile	Gln 200	Gly	Asp	Gly	Ala	Ala 205	Leu	Gln	Glu
Lys	Leu 210	Cys	Ala	Thr	Tyr	Lys 215	Leu	Cys	His	Pro	Glu 220	Glu	Leu	Val	Leu
Leu 225	Gly	His	Ser	Leu	Gly 230	Ile	Pro	Trp	Ala	Pro 235	Leu	Ser	Ser	Cys	Pro 240
Ser	Gln	Ala	Leu	Gln 245	Leu	Ala	Gly	Cys	Leu 250	Ser	Gln	Leu	His	Ser 255	Gly
Leu	Phe	Leu	туг 260	Gln	Gly	Leu	Leu	Gln 265	Ala	Leu	Glu	Gly	Ile 270	Ser	Pro
Glu	Leu	Gly 275	Pro	Thr	Leu	Asp	Thr 280	Leu	Gln	Leu	Asp	Val 285	Ala	Asp	Phe
Ala	Thr 290	Thr	Ile	Trp	Gln	Gln 295	Met	Glu	Glu	Leu	Gly 300	Met	Ala	Pro	Ala
Leu 305	Gln	Pro	Thr	Gln	Gly 310	Ala	Met	Pro	Ala	Phe 315	Ala	Ser	Ala	Phe	Gln 320
Arg	Arg	Ala	Gly	Gly 325	Va1	Leu	Val	Ala	Ser 330	His	Leu	Gln	Ser	Phe 335	Leu
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<211>

349

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Gln Pro	Pro Leu 20	Pro L	eu Leu	Asp	Phe 25	Asn	Asn	Leu	Asn	Gly 30	Glu	Asp
Gln Asp	Ile Leu 35	Met G	lu Asn	Asn 40	Leu	Arg	Arg	Pro	Asn 45	Leu	Glu	Ala
Phe Asn 50	Arg Ala	Val L	ys Ser 55	Leu	Gln	Asn	Ala	Ser 60	Ala	Ile	Glu	Ser
Ile Leu 65	Lys Asn	Leu L 7		Cys	Leu	Pro	Leu 75	Ala	Thr	Ala	Ala	Pro 80
Thr Arg	His Pro	Ile H 85	is Ile	Lys	Asp	Gly 90	Asp	Trp	Asn	Glu	Phe 95	Ala
Arg Lys	Leu Thr 100		yr Leu	Lys	Thr 105	Leu	Glu	Asn	Ala	Gln 110	Ala	Gln
Gln Tyr	Val Ile 115	Glu G	ly Arg	Ile 120	Ser	Pro	Gln	Pro	Pro 125	Val	Asn	Ala
Gly Gly 130	Gly Ser	Gly G	ly Gly 135	Ser	Gly	Gly	Gly	Ser 140	Glu	Gly	Gly	Gly
Ser Glu 145	Gly Gly		er Glu 50	Gly	Gly	Gly	Ser 155	Glu	Gly	Gly	Gly	Ser 160
Gly Gly	Gly Ser	Gly S 165	er Gly	Asp	Phe	Asp 170	Tyr	Glu	Asn	Met	Ala 175	Thr
Pro Leu	Gly Pro 180	Ala S	er Ser	Leu	Pro 185	Gln	Ser	Phe	Leu	Leu 190	Lys	Ser
Leu Glu	Gln Val 195	Arg L	ys Ile	Gln 200	Gly	Asp	Gly	Ala	Ala 205	Leu	Gln	Glu
Lys Leu 210	Cys Ala	Thr T	yr Lys 215	Leu	Cys	His	Pro	Glu 220	Glu	Leu	Val	Leu
Leu Gly 225	His Ser		ly Ile 30	Pro	Trp	Ala	Pro 235	Leu	Ser	Ser	Cys	Pro 240
Ser Gln	Ala Leu	Gln L 245	eu Ala	Gly	Cys	Leu 250	Ser	Gln	Leu	His	Ser 255	Gly
Leu Phe	Leu Tyr 260	Gln G	ly Leu	Leu	Gln 265	Ala	Leu	Glu	Gly	Ile 270	Ser	Pro
Glu Leu	Gly Pro 275	Thr L	eu Asp	Thr 280	Leu	Gln	Leu	Asp	Val 285	Ala	Asp	Phe
Ala Thr 290	Thr Ile	Trp G	ln Gln 295	Met	Glu	Glu	Leu	Gly 300	Met	Ala	Pro	Ala
Leu Gln 305	Pro Thr		ly Ala 10	Met	Pro	Ala	Phe 315	Ala	Ser	Ala	Phe	Gln 320
Arg Arg	Ala Gly	Gly V	al Leu	Val	Ala	Ser 330	His	Leu	Gln	Ser	Phe 335	Leu
Glu Val	Ser Tyr 340	Arg V	al Leu	Arg	His 345	Leu	Ala	Gln	Pro			

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<210> 344 <211> 322

PRT <212> Artificial Sequence <220> MUTAGEN <221> <222> 1-322 <223> <400> 344 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Ser Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 135 Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 235 Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu 265 Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe 280 Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 349 <211>

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<212>

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307 <211> <212> PRT Artificial Sequence <220> <221> MUTAGEN <222> 1-307 <223> <400> 346 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 10 Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 120 Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln 135 Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 185 Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln 235 Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 305

<210> 347 <211> 322 <212> PRT

<213>	Art	ific	cial	Seq	lence	e								
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<400>	347	7												
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Gln Asp	Ile 35	Leu	Met	Glu	Asn	Asn 40	Leu	Arg	Arg	Pro	Asn 45	Leu	Glu	Ala
Phe Asn 50	Arg	Ala	Val	Lys	Ser 55	Leu	Gln	Asn	Ala	Ser 60	Ala	Ile	Glu	Ser
Ile Leu 65	Lys	Asn	Leu	Leu 70	Pro	Cys	Leu	Pro	Leu 75	Ala	Thr	Ala	Ala	Pro 80
Thr Arg	His	Pro	11e 85	His	Ile	Lys	Asp	Gly 90	Asp	Trp	Asn	Glu	Phe 95	Arg
Arg Lys	Leu	Thr 100	Phe	Tyr	Leu	Val	Thr 105	Leu	Glu	Asn	Ala	Gln 110	Ala	Gln
Gln Tyr	Val 115	Ile	Glu	Gly	Arg	Ile 120	Ser	Pro	Gly	Glu	Pro 125	Ser	Gly	Pro
Ile Ser 130	Thr	Ile	Asn	Pro	Ser 135	Pro	Pro	Ser	Lys	Glu 140	Ser	His	Lys	Ser
Pro Asn 145	Met	Ala	Thr	Pro 150	Leu	Gly	Pro	Ala	Ser 155	Ser	Leu	Pro	Gln	Ser 160
Phe Leu	Leu	Lys	Cys 165	Leu	Glu	Gln	Val	Arg 170	Lys	Ile	Gln	Gly	Asp 175	Gly
Ala Ala	Leu	Gln 180	Glu	Lys	Leu	Cys	Ala 185	Thr	Tyr,	Lys	Leu	Cys 190	His	Pro
Glu Glu	Leu 195	Val	Leu	Leu	Gly	His 200	Ser	Leu	Gly	Ile	Pro 205	Trp	Ala	Pro
Leu Ser 210	Ser	Cys	Pro	Ser	Gln 215	Ala	Leu	Gln	Leu	Ala 220	G1y	Cys	Leu	Ser
Gln Leu 225	His	Ser	Gly	Leu 230	Phe	Leu	Tyr	Gln	Gly 235	Leu	Leu	Gln	Ala	Leu 240
Glu Gly	Ile	Ser	Pro 245	Glu	Leu	Gly	Pro	Thr 250	Leu	Asp	Thr	Leu	Gln 255	Leu
Asp Val	Ala	Asp 260	Phe	Ala	Thr	Thr	Ile 265	Trp	Gln	Gln	Met	Glu 270	Glu	Leu
Gly Met	Ala 275	Pro	Ala	Leu	Gln	Pro 280	Thr	Gln	Gly	Ala	Met 285	Pro	Ala	Phe
Ala Ser 290	Ala	Phe	Gln	Arg	Arg 295	Ala	Gly	Gly	Val	Leu 300	Val	Ala	Ser	His
Leu Gln 305	Ser	Phe	Leu	Glu 310	Val	Ser	Tyr	Arg	Val 315	Leu	Arg	His	Leu	Ala 320
Gln Pro														
<210> <211> <212> <213>	348 349 PRI Art	?	ial	Sequ	ience	e								

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       1-307
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Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys
                                    10
Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp
Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala
Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser
Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro
Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg
Arg Lys Leu Thr Phe Tyr Leu Trp Thr Leu Glu Asn Ala Gln Ala Gln
Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly
Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln
                       135
Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp
Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His
Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala
                               185
Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu
Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala
Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln
                                       235
Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu
Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala
Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser
His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu
Ala Gln Pro
<210>
<211>
        322
<212>
        PRT
<213>
      Artificial Sequence
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315/348

<212>

PRT

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<210> 354 <211> 349 <212> PRT <213> Artificial Sequence

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MUTAGEN <221> <222> 1-322 <223> <400> 356 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu His Thr Leu Glu Asn Ala Gln Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 357 <211> 349 <212> PRT <213> Artificial Sequence

320/348

<220>

<221>

MUTAGEN

<222> 1-349 <223>

<400> 357

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro

Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg

Arg Lys Leu Thr Phe Tyr Leu His Thr Leu Glu Asn Ala Gln Ala Gln

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala

Gly Gly Gly Ser Gly Gly Gly Gly Gly Gly Ser Glu Gly Gly

Ser Glu Gly Gly Ger Glu Gly Gly Gly Ser Glu Gly Gly Ser

Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr

Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser 1.85

Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu

Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu

Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro

Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly

Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro

Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 280

Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala

Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln

Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu

Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro

<210> 358

<211>

PRT <212>

<213> Artificial Sequence

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<220> <221> MUTAGEN

<222> 1-322 <223>

<400> 359

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 1 5 10 15

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 20 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 55 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg

Arg Lys Leu Thr Phe Tyr Leu Phe Thr Leu Glu Asn Ala Gln Ala Gln 100 105 110

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro
115 120 125

Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 130 135 140

Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser 145 150 155 160

Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly 165 170 175

Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 180 185 190

Glu Glu Leu Val Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 195 200 205

Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 210 215 220

Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 225 230 235 240

Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu 245 250 255

Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu 260 265 270

Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe

Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His 290 295 300

Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala 305 310 315 320

Gln Pro

<210> 360

<211> 349

<212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN

<222> 1-349

<223>

<400> 360

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 1 5 10 15

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 20 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 55 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Phe Thr Leu Glu Asn Ala Gln Ala Gln 100 105 110

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Gly Gly 130 135 140

Ser Glu Gly Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser 145 150 155 160

Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr 165 170 175

Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser 180 185 190

Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu 195 200 205

Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu 210 215 220

Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro 225 230. 235 240

Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly 245 250 255

Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro 260 265 270

Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 275 280 285

Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala 290 295 300

Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln 305 310 315 320

Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu 325 330 335

Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 340 345

<210> 361

<211> 307 <212> PRT

<213> Artificial Sequence

<220>

MUTAGEN <221> <222> 1-307 <223> <400> 361 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala, Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Tyr Thr Leu Glu Asn Ala Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 115 120 . 125 Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp 150 Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 200 Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 215 Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 265 Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 305 <210> 362 322 <212> PRT Artificial Sequence <213>

<220> <221>

<222>

MUTAGEN 1-322

<223>

<400> 362

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 1 5 10 15

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 55 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Tyr Thr Leu Glu Asn Ala Gln Ala Gln 100 105 110

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 115 120 125

Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 130 135 140

Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser 145 150 155 160

Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly 165 170 175

Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 180 185 190

Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 195 $200\,$ 205

Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 210 215 220

Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 225 230 235 240

Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu 245 250 255

Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu 260 265 270

Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe 275 280 285

Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His 290 295 300

Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala 305 310 315 320

Gln Pro

<210> 363

<211> 349

<212> PRT <213> Artificial Sequence

<220>

<221> MUTAGEN

<222> 1-349

<223>

<400> 363

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 1 5 10 15

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 20 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 55 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Tyr Thr Leu Glu Asn Ala Gln Ala Gln 100 105 110

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala 115 120 125

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Gly Gly Gly 130 135

Ser Glu Gly Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser 145 150 150 160

Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr 165 170 175

Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Lys Ser 180 185 190

Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu 195 200 205

Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu 210 215 220

Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro 225 230 235 240

Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly 245 250 255

Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro 260 265 270

Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 275 280 285

Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala 290 295 300

Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln

Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu 325 330 335

Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 340 345

<210> 364

<211> 307 <212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN

<222> 1-307 <400> 364 Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 40 Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ile Gln Ala Gln 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp 155 Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His 170 Pro Glu Glu Leu Val Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 265 Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu

Ala Gln Pro 305

<223>

<210> 365 <211> 322 <212> PRT <213> Artificial Sequence <220> <221> MUTAGEN <222> 1-322

<400> 365

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 10

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro

Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ile Gln Ala Gln

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 120

Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 135

Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser

Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly

Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 185

Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro

Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser

Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 230

Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu 250

Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu

Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe

Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His

Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala 315

Gln Pro

<210> 366

<211> 349 <212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN 1-349

<222>

<223>

<400> 366

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 20 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ile Gln Ala Gln 100 105 110

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala . 115 120 125

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Gly Gly 130 135 140

Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser 145 155 160

Gly Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr

Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser 180 185 190

Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu
195 200 205

Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu 210 215 220

Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro 225 230 235 240

Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly 245 250 255

Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro 260 265 270

Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 275 280 285

Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala 290 295 300

Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln 305 310 315 320

Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu 325 330 335

Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 340 345

<210> 367 <211> 307

<212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN <222> 1-307

<223>

<400> 367

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 1 5 10 15

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 20 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 55 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Ile Ala Gln
100 105 110

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 115 120 125

Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln 130 135 140

Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp 145 150 155 160

Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His $165 \,\,$ $170 \,\,$ $175 \,\,$

Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 180 185 190

Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 195 200 205

Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 210 215 220

Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln 225 230 235 240

Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu 245 250 255

Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 260 265 270

Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser 275 280 285

His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 290 295 300

Ala Gln Pro 305

<210> 368 <211> 322

<211> 322 <212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN

<222> 1-322

<223>

<400> 368

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 1 5 10 15

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 20 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 55 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Ile Ala Gln 100 105 110

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 115 120 125

Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser 130 135 140

Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser 145 150 155 160

Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly 165 170 175

Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro 180 185 190

Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 195 200 205

Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 210 215 220

Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 225 230 235 240

Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu 245 250 255

Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu 260 265 270

Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe 275 280 285

Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His 290 295 300

Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala 305 310 315 320

Gln Pro

<210> 369

<211> 349 <212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN <222> 1-349

<223>

<400> 369

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 10 Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Ile Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gln Pro Pro Val Asn Ala Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Ser Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Asn Met Ala Thr 170 Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Ser 185 Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe 280 Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala 295 Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro 340 345 <210> 370 <211> 307 <212> PRT Artificial Sequence <213> <220> MUTAGEN <221> <222> 1-307

<400> 370

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 20 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala $35 \hspace{1cm} 40 \hspace{1cm} 45$

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 . 55 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Phe Ala Gln 100 105 110

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 115 120 125

Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln 130 135 140

Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp 145 150 150 160

Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His 165 170 175

Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 180 185 190

Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 195 200 205

Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 210 215 220

Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln 225 230 230 240

Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu 245 250 255

Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala 260 265 270

Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser

His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 290 295 300

Ala Gln Pro 305

<210> 371

<211> 322 <212> PRT

<213> Artificial Sequence

<220>

<221> MUTAGEN <222> 1-322

<223>

<400> 371

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Phe Ala Gln Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly 170 Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 215 Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu 230 Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu 265 Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe 280 Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 372 <211> 349 <212> PRT <213> Artificial Sequence <220> MUTAGEN <221> <222> 1-349 <223> <400> 372

Met 1	Ala	Asn	Cys	Ser 5	Asn	Met	Ile	Asp	Glu 10	Ile	Ile	Thr	His	Leu 15	Lys
Gln	Pro	Pro	Leu 20	Pro	Leu	Leu	Asp	Phe 25	Asn	Asn	Leu	Asn	Gly 30	Glu	Asp
Gln	Asp	Ile 35	Leu	Met	Glu	Asn	Asn 40	Leu	Arg	Arg	Pro	Asn 45	Leu	Glu	Ala
Phe	Asn 50	Arg	Ala	Val	Lys	Ser 55	Leu	Gln	Asn	Ala	Ser 60	Ala	Ile	Glu	Ser
Ile 65	Leu	Lys	Asn	Leu	Leu 70	Pro	Cys	Leu	Pro	Leu 75	Ala	Thr	Ala	Ala	Pro 80
Thr	Arg	His	Pro	Ile 85	His	Ile	Lys	Asp	Gly 90	Asp	Trp	Asn	Glu	Phe 95	Arg
Arg	Lys	Leu	Thr 100	Phe	Tyr	Leu	Lys	Thr 105	Leu	Glu	Asn	Ala	Phe 110	Ala	Gln
Gln	Tyr	Val 115	Ile	Glu	Gly	Arg	Ile 120	Ser	Pro	Gln	Pro	Pro 125	Val	Asn	Ala
Gly	Gly 130	Gly	Ser	Gly	Gly	Gly 135	Ser	Gly	Gly	Gly	Ser 140	Glu	Gly	Gly	Gly
Ser 145	Glu	Gly	Gly	Gly	Ser 150	Glu	Gly	Gly	Gly	<i>Ser</i> 155	Glu	Gly	Gly	Gly	Ser 160
Gly	Gly	Gly	Ser	Gly 165	Ser	Gly	Asp	Phe	Asp 170	Tyr	Glu	Asn	Met	Ala 175	Thr
Pro	Leu	Gly	Pro 180	Ala	Ser	Ser	Leu	Pro 185	Gln	Ser	Phe	Leu	Leu 190	Lys	Ser
Leu	Glu	Gln 195	Val	Arg	Lys	Ile	Gln 200	Gly	Asp	Gly	Ala	Ala 205	Leu	Gln	Glu
Lys	Leu 210	Cys	Ala	Thr	Tyr	Lys 215	Leu	Cys	His	Pro	Glu 220	Glu	Leu	Val	Leu
Leu 225	Gly	His	Ser	Leu	Gly 230	Ile	Pro	Trp	Ala	Pro 235	Leu	Ser	Ser	Суз	Pro 240
Ser	Gln	Ala	Leu	Gln 245	Leu	Ala	Gly	Cys	Leu 250	Ser	Gln	Leu	His	Ser 255	Gly
Leu	Phe	Leu	Туr 260	Gln	Gly	Leu	Leu	Gln 265	Ala	Leu	Glu	Gly	Ile 270	Ser	Pro
Glu	Leu	Gly 275	Pro	Thr	Leu	Asp	Thr 280		Gln	Leu	Asp	Val 285		Asp	Phe
Ala	Thr 290	Thr	Ile	Trp	Gln	Gln 295	Met	Glu	Glu	Leu	Gly 300	Met	Ala	Pro	Ala
Leu 305	Gln	Pro	Thr	Gln	Gly 310	Ala	Met	Pro	Ala	Phe 315	Ala	Ser	Ala	Phe	Gln 320
Arg	Arg	Ala	Gly	Gly 325	Val	Leu	Val	Ala	Ser 330	His	Leu	Gln	Ser	Phe 335	Leu
Glu	Val	Ser	Туr 340	Arg	Val	Leu	Arg	His 345	Leu	Ala	Gln	Pro			
<210> 373 <211> 307 <212> PRT <213> Artificial		cial	Sequ	ience	ì										
<220> <221> MUTAGEN <222> 1-307 <223>		1													

<400> 373

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys 1 $$ 5 $$ 10 $$ 15

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp 20 25 30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala 35 40 45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser 50 55 60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro 65 70 75 80

Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg 85 90 95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Met Gln 100 105 110

Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Gly Gly Ser Gly Gly 115 120 125

Gly Ser Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln 130 135 140

Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp 145 150 155 160

Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His 165 170 175

Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala 180 185 190

Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu 195 200 205

Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala 210 215 220

Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln 225 230 235 240

Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu 245 250 255

Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala

Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser 275 280 285

His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu 290 295 300

Ala Gln Pro 305

<210> 374

<211> 322

<212> PRT <213> Artificial Sequence

<220>

<221> MUTAGEN

<222> Holds

<223>

<400> 374

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg $\hbox{Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Met Gln}$ 105 Gln Tyr Val Ile Glu Gly Arg Ile Ser Pro Gly Glu Pro Ser Gly Pro 120 Ile Ser Thr Ile Asn Pro Ser Pro Pro Ser Lys Glu Ser His Lys Ser Pro Asn Met Ala Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro 200 Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser 215 Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro <210> 375 <211> 349 <212> PRT <213> Artificial Sequence <220> MUTAGEN <221> <222> 1-349 <223> <400> Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys

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Phe	Asn 50	Arg	Ala	Val	Lys	Ser 55	Leu	Gln	Asn	Ala	Ser 60	Ala	Ile	Glu	Ser
Ile 65	Leu	Lys	Asn	Leu	Leu 70	Pro	Cys	Leu	Pro	Leu 75	Ala	Thr	Ala	Ala	Pro 80
Thr	Arg	His	Pro	Ile 85	His	Ile	Lys	Asp	Gly 90	Asp	Trp	Asn	Glu	Phe 95	Arg
Arg	Lys	Leu	Thr 100	Phe	Tyr	Leu	Lys	Thr 105	Leu	Glu	Asn	Ala	Gln 110	Ala	Gln
Gln	Tyr	Val 115	Ile	Glu	Gly	Arg	Ile 120	Ser	Pro	Gln	Pro	Pro 125	Val	Asn	Ala
Gly	Gly 130	Gly	Ser	Gly	Gly	Gly 135	Ser	Gly	Gly	Gly	Ser 140	Glu	Gly	Gly	Gly
Ser 145	Glu	Gly	Gly	Gly	Ser 150	Glu	Gly	Gly	Gly	Ser 155	Glu	Gly	Gly	Gly	Ser 160
Gly	Gly	Gly	Ser	Gly 165	Ser	Gly	Asp	Phe	Asp 170	Tyr	Glu	Asn	Met	Ala 175	Thr
Pro	Leu	Gly	Pro 180	Ala	Ser	Ser	Leu	Pro 185	Gln	Ser	Phe	Leu	Leu 190	Lys	Ser
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Lys	Leu 210	Cys	Ala	Thr	Tyr	Lys 215	Leu	Cys	His	Pro	Glu 220	Glu	Leu	Val	Leu
Leu 225	Gly	His	Ser	Leu	Gly 230	Ile	Pro	Trp	Ala	Pro 235	Leu	Ser	Ser	Cys	Pro 240
Ser	Gln	Ala	Leu	Gln 245	Leu	Ala	Gly	Суз	Leu 250	Ser	Gln	Leu	His	Ser 255	Gly
Leu	Phe	Leu	туr 260	Gln	Gly	Leu	Leu	Gln 265	Ala	Leu	Glu	Gly	Ile 270	Ser	Pro
Glu	Leu	Gly 275	Pro	Thr	Leu	Asp	Thr 280	Leu	Gln	Leu	Asp	Val 285	Ala	Asp	Phe
Ala	Thr 290	Thr	Ile	Trp	Gln	Gln 295	Met	Glu	Glu	Leu	Gly 300	Met	Ala	Pro	Ala
Leu 305	Gln	Pro	Thr	Gln	Gly 310	Ala	Met	Pro	Ala	Phe 315	Ala	Ser	Ala	Phe	Gln 320
Arg	Arg	Ala	Gly	Gly 325	Val	Leu	Val	Ala	Ser 330	His	Leu	Gln	Ser	Phe 335	Leu
Glu	Val	Ser	Tyr 340	Arg	Va1	Leu	Arg	His 345	Leu	Ala	Gln	Pro			

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A61K 47/48,

(74) Agent: BAUER, S., Christopher; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US).

(21) International Application Number: PCT/US01/11256

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- (71) Applicant (for all designated States except US): PHAR-MACIA CORPORATION [US/US]; P.O. Box 5110, Chicago, IL 60680-5110 (US).
- (71) Applicants and
- (72) Inventors: FINN, Rory [US/US]; 976 Sunburst Court, Manchester, MO 63021 (US). GOKARN, Yatin [US/US]; 1501 Maple Avenue, Apt. 606, Evanston, IL 60201 (US). HILLS, Robert [US/US]; 1620 Summers End Lane, Fenton, MO 63026 (US). NICASTRO, Peter [US/US]; 1904 Hurstgreen Avenue, Overland, MO 63114-5736 (US). QI, Hong [US/US]; 4529 Concord Lane, Northbrook, IL 60062 (US). SEDO, Kurt [US/US]; 4515 N. Rockwell Street, Chicago, IL 60625 (US). SIEGEL, Ned [US/US]; 312 N. Powder Mill Road, Belleville, IL 62223-1153 (US). WALTER, Smith [US/US]; 2603 Greenbuar Estates Courts, St. Louis, MO 63122 (US).

- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
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(54) Title: CHEMICALLY-MODIFIED MYELOPOIETIN CONJUGATES

(57) Abstract: The present invention provides a chemically modified Myelopoietin (MPO) prepared by binding a water soluble polymer to the protein. The chemically-modified protein according to the present invention may have a much longer lasting neutrophil-increasing activity than that of the un-modified MPO, enabling reduced dose and scheduling opportunities.

INTERNATIONAL SEARCH REPORT

Inter >nal Application No PCT/US 01/11256

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K47/48 C07K C07K14/54 A61P7/00 A61P37/06 A61P37/02 According to International Patent Classification (IPC) or to both national classification and IPC **B. FIELDS SEARCHED** Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07K A61K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, CHEM ABS Data, MEDLINE, EMBASE C. DOCUMENTS CONSIDERED TO BE RELEVANT Category ° Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. χ WO 90 12874 A (GENETICS INSTITUTE INC.) 1.7 - 361 November 1990 (1990-11-01) claims 1-14 page 13, line 20 -page 14, line 18 page 16, line 12 - line 29 Υ 2-6 WO 95 21197 A (G.D. SEARLE &CO.) Υ 2-6 10 August 1995 (1995-08-10) cited in the application claims 1-13 US 6 022 535 A (S. C. BAUER ET AL) Υ 1-36 8 February 2000 (2000-02-08) cited in the application claims 1-62 χ Further documents are listed in the continuation of box C. X Patent family members are listed in annex. ° Special categories of cited documents: *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the "A" document defining the general state of the art which is not considered to be of particular relevance invention *E* earlier document but published on or after the international "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such docu-"O" document referring to an oral disclosure, use, exhibition or ments, such combination being obvious to a person skilled document published prior to the international filing date but later than the priority date claimed "&" document member of the same patent family Date of the actual completion of the international search Date of mailing of the international search report 20 February 2002 04/03/2002 Name and mailing address of the ISA Authorized officer European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,

Fax: (+31-70) 340-3016

Siatou, E

INTTRNATIONAL SEARCH REPORT

Inter onal Application No PCT/US 01/11256

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	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	 In.
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Α	WO 94 12639 A (G.D. SEARLE ET AL) 9 June 1994 (1994-06-09) claims 1-21	1-36
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information on patent family members

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